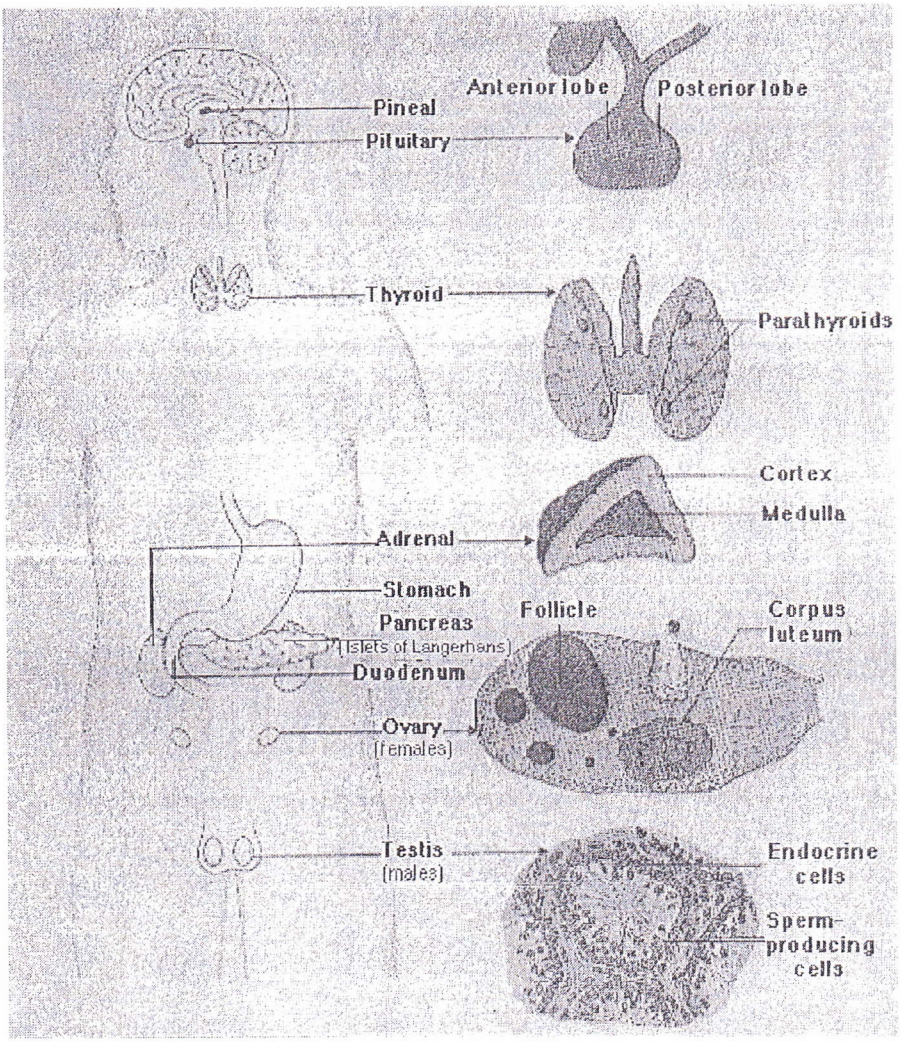

Pediatric Endocrinology

By

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2010

Pituitary Gland

(The master gland)

Anterior Pituitary

Somatotropes ⟶ GH (191 aa)
Lactotropes ⟶ Prolactin (199 aa)
Thyrotropes ⟶ TSH (Thyrotropin)
Coticotropes ⟶ ACTH (Corticotropin)
Gonadotropes ⟶ FSH, LH

These hormones are under the control of:

- Hypothalamic neurohormones: via the hypothalamo-hypophyseal portal circulation
- Feedback control

Posterior Pituitary (Neural hormones)

ADH (arginine vasopressin)
Oxytocin

These hormones are **synthesized** in supraoptic & paraventricular nuclei of the hypothalamus and **transmitted** via the axoplasm to be **stored** in the posterior pituitary.

Growth Hormone

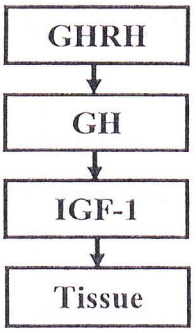
- **Pulsatile** secretion more with sleep
- Action is **mediated** by insulin like growth factor-1 ***(IGF-1)*** or "somatomedin C" formed by the liver
- **Action:**
  1. **Growth:** ↑↑ Size of various tissues (bones, cartilage, muscles& viscera).
  2. **Proteins:** Anabolic.
  3. **CHO:** ↑↑ Gluconeogenesis.
  4. **Lipids:** ↑↑ Lipolysis.
  5. **Electrolytes:** ↑↑ Ca, ↑↑ Na, ↑↑ PO_4
- **Control of GH secretion:**

Increase	Decrease
GHRH (GH-releasing hormone)	Somatostatin (also ↓↓ insulin, glucagon, gastrin, VIP)
Synthetic GHRH	Synthetic somatostatin analog ***(Octreotide)***
Hypoglycemia (Insulin)	Hyperglycemia
↑↑ aa (e.g., arginine)	
Clonidine, L-dopa, Glucagon	
Stress, Sleep, Exercise, Fasting	

Hypopituitarism

Definition

It is deficiency of GH with or without other pituitary hormones

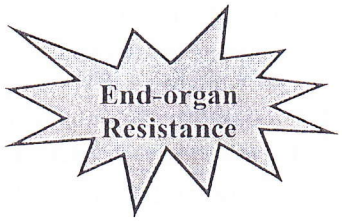


Etiology

I) Isolated GH deficiency:

A) Genetic

- GHRH receptor gene mutation
- GH gene mutation (AR, AD or X-linked)
- Biologically inactive GH
- GH receptor gene mutation ***(Laron syndrome)***: Autosomal recessive [↑↑ GH, ↓↓ IGF-1, No response to exogenous GH]
- IGF-1 gene mutation



B) Acquired

- Radiotherapy (leukemia)
- Idiopathic

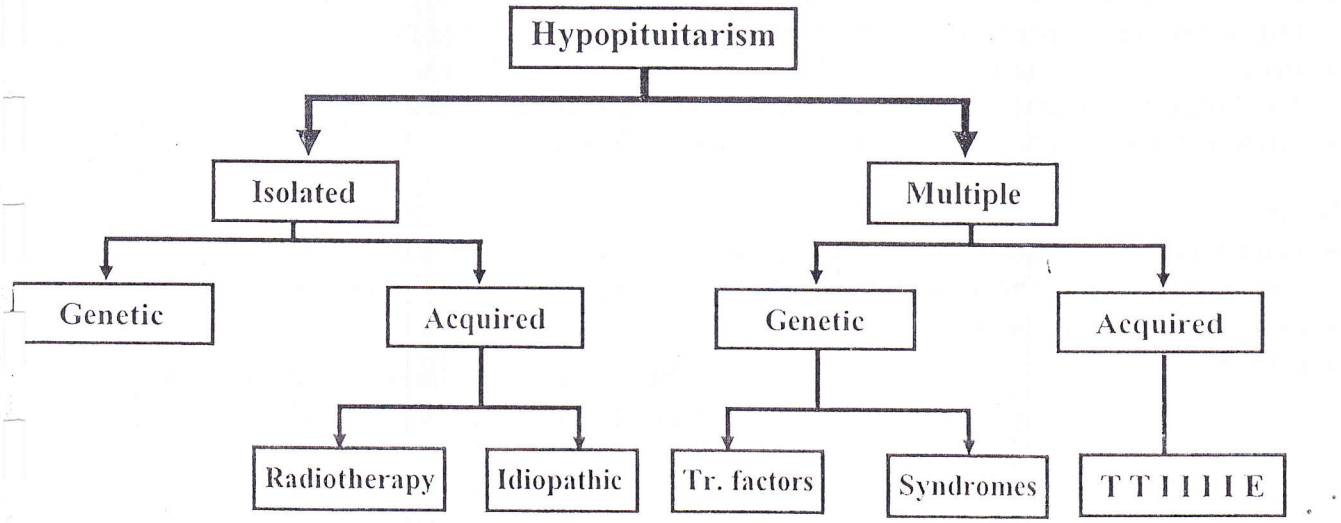
II) Multiple pituitary hormone deficiency:

A) Genetic

- Mutations of transcription factors ⟶ Failure of transcription e.g. PROP1, LHX3, LHX4 gene mutation
- Congenital absence of the pituitary gland
- Anencephaly, encephalocele& hydrocephalus
- Septo-optic dysplasia (optic n. dysplasia& maldevelopment of septum pellucidum)
- Holoprosencephaly

B) Acquired

- Trauma: birth injury, child abuse, fracture base of skull, surgery
- Tumors: Craniopharyngioma, adenoma, germinoma, optic glioma
- Irradiation (GH deficiency precedes other hormones)
- Infection: meningitis & encephalitis
- Infiltration: histiocytosis X, hemochromatosis, sarcoidosis, TB, Toxoplasmosis
- Immune hypophysitis
- Empty-sella syndrome: congenital or following surgery or irradiation



Clinical picture

A) Congenital Hypopituitarism:

1. At Birth:

- Normal weight & height
- Neonatal emergencies: apnea, cyanosis, hypoglycemia, seizures
- Prolonged neonatal jaundice (Conjugated)
- Microphallus in male is an important **diagnostic** clue

2. Infancy& childhood:

- Profound proportionate postnatal growth failure (>2 SD below the mean for age & sex)
- Facies: rounded head, short face, prominent forehead, depressed nasal bridge, small nose, underdeveloped mandible, teeth (Delayed eruption & crowded)
- Intelligence: usually normal
- Sexual maturation: may be delayed
- Hypoglycemia (10%)

B) Acquired Hypopituitarism:

1. Hormonal manifestations:

- The child is normal initially
- Gradual onset& progressive course of growth failure
- Hypofunction of thyroid, adrenals and gonads
- Diabetes insipidus

2. C/P of the cause:

- Pressure symptoms: ↑↑ ICT, optic atrophy, visual field defects, seizures
- Trauma, infection…

Investigations

*Thyroid hormones are necessary for GH synthesis & action; so must be assessed **before** GH studies.*

A) Laboratory:

1. GH plasma level

GH level < 10 ng/ mL after **2** provocative tests is diagnostic

- Physiologic stimulation: Sleep (60 min), Exercise (20 min) ??
- Provocative agents: Insulin, clonidine, arginine, glucagon, L-dopa

Measuring GH level every 20 min over (12-24 hr) is used to diagnose ***GH neurosecretory dysfunction.***

2. **IGF-1:** ↓↓ in all cases but ↑↑ with GH administration (except in Laron syndrome)
3. **Other pituitary hormones:** ACTH, TSH, ADH, Cortisol, T_3, T_4 (Not FSH & LH)
4. **Prolactin:** Hyperprolactinemia strongly suggests hypothalamic lesion.
5. **TRH stimulation test:** ↑↑TSH& prolactin suggests hypothalamic lesion.
6. **GHRH stimulation test:** ↑↑GH suggests hypothalamic lesion.

B) Imaging:

- **Skull X-ray:** beaten silver appearance, separation of sutures, enlargement of sella, destruction of clinoid processes& IC calcification (bone defects in histiocytosis)
- **Long bones:** delayed bone age.
- CT& MRI

In hypothalamic lesions: ↓↓ all anterior pituitary hormones except prolactin

Treatment

1. **Treatment of the cause:** Surgery for tumors.
2. **Replacement of pituitary hormones:** Thyroid, hydrocortisone & late sex hormones.
3. **Recombinant human GH (rHuGH)**
   - ***Dose:*** 0.18-0.3 mg/kg/week, SC in 6-7 divided doses.
   - ***Duration:*** continuous till closure of epiphyses (NB: ***leoprolide*** may be used to delay puberty).

Criteria for stopping Rx:

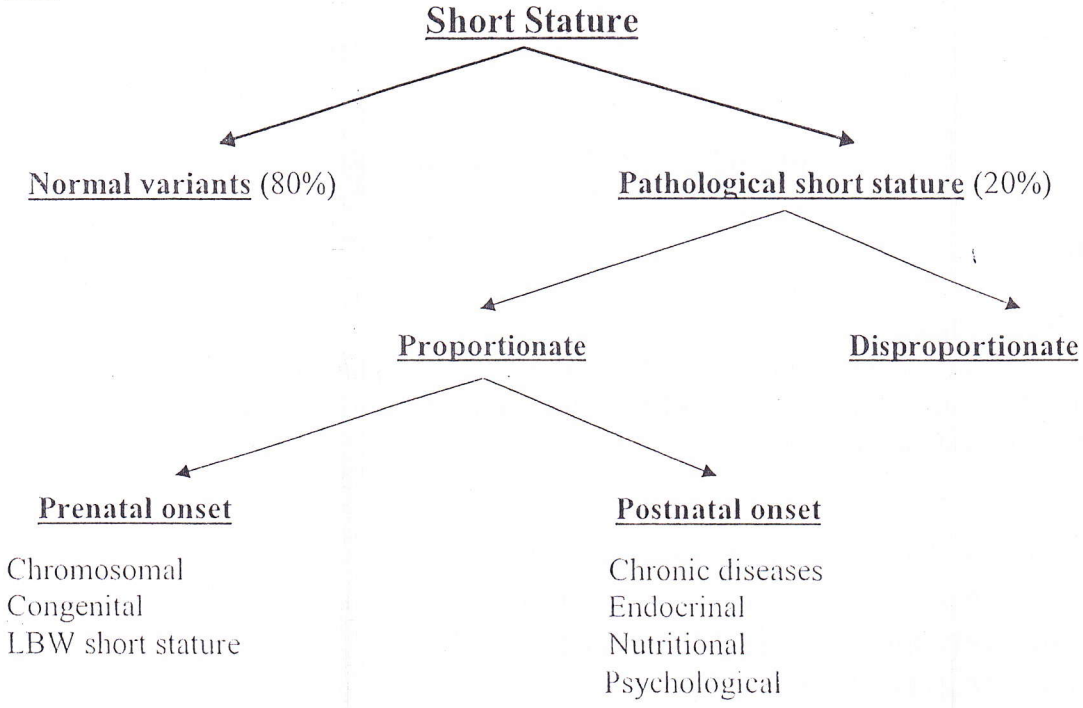
- Growth rate < 1 inch/year
- Bone age >14 yr in ♀ & >16 yr in ♂

- *Side effects:*
  - Leukemia.
  - Hypothyroidism
  - Pseudotumor cerebri
  - Gynecomastia
  - Slipped capital femoral epiphyses, worsening of scoliosis.
  - Development of anti-GH antibodies (Rx with IGF-1)

- *Other indications of hGH:*
  - Turner syndrome
  - Noonan syndrome
  - ESRD
  - Prader-Willi $
  - Silver-Russel $
  - IUGR
  - Skeletal dysplasia
  - Juvenile rheumatoid arthritis.
  - Familial short stature (some patients may benefit)

4. **GHRH in hypothalamic causes.**
5. **Recombinant IGF-1:** in Laron $ & with the development of anti-GH antibodies

DD Short stature.



Short Stature

Definition

Height more than 2 SD below the mean height for age & sex or < 5th percentile.
Pathologic short stature: Height >3 SD below the mean height for age& sex.

Nomenclatures

Lower segment: Measured from the upper border of the symphysis pubis to the floor.

Upper segment: Total height – lower segment.

Arm span: Distance between the tips of middle fingers when the arms are fully extended.

Supine length: (birth to 2-3 yrs).The child is measured on his back by 2 individuals with appropriate equipment with fixed headboard & movable footboard. The head should be in the "Frankfurt plane" (ear hole to lower border of eye socket).

Standing height: measured against an appropriate vertical measure with the heels together and buttocks & shoulder plates touching the vertical and the head in "Frankfurt plane".

U/L ratio:

- **At birth:** 1.7 (Umbilicus is in the middle)
- **At 3 yrs:** 1.3
- **At 7 yrs:** 1 (Symphysis is in the middle)

Arm span – height:

- 1st 7 yrs: –3
- 8 -12 yrs: Zero

Classification

A) Proportionate or Disproportionate

1. **Proportionate short stature:** normal values are obtained
2. **Disproportionate short stature:** abnormal values are obtained

B) Type of short stature

1. **Short limbs**
2. **Short trunk**

Ratio	Short Limbs	Short Trunk
U/L	High	Low
Arm span/Height	Low	High

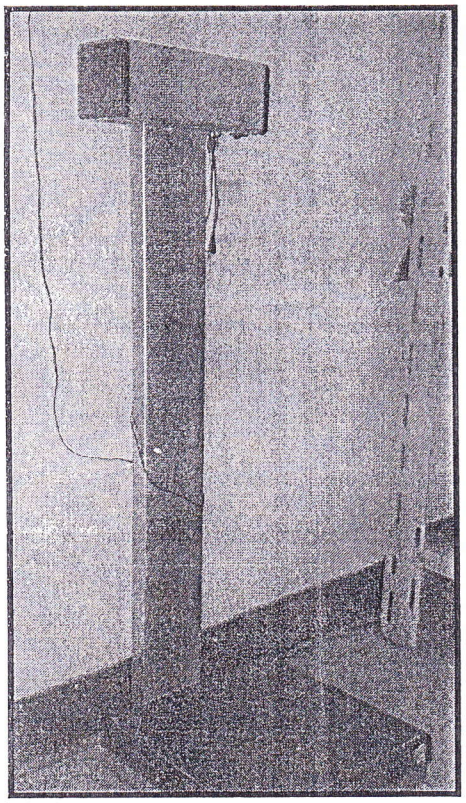
C) Classification of short limbs

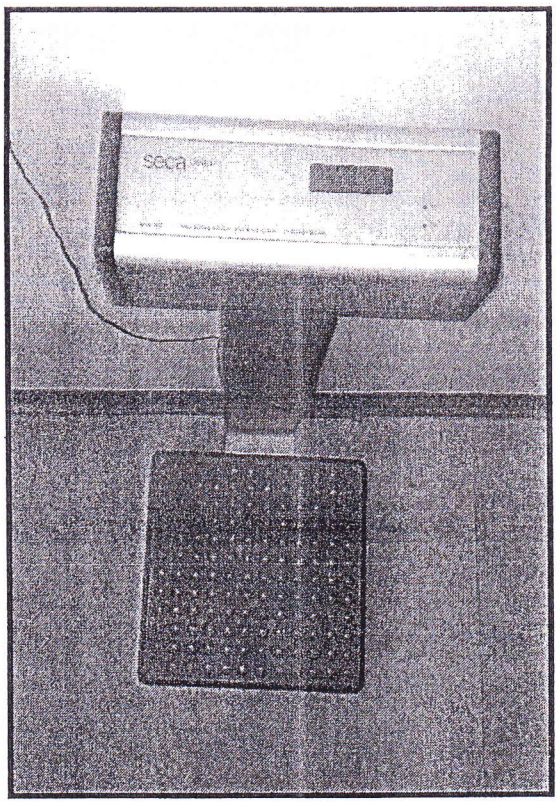
1. **Rizomelic:** proximal shortening of humerus & femur (e.g., achondroplasia)
2. **Mesomelic:** middle segment shortening of radius& ulna, tibia& fibula.
3. **Acromelic:** terminal shortening of fingers.

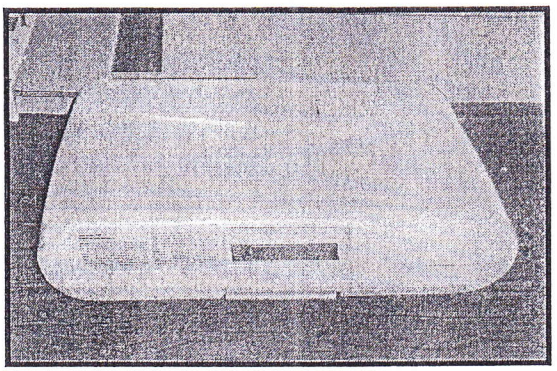
MPH & TCR

Mean parental height = (Father's height + Mother's height) / 2
Mid Parental Height (MPH) for ♂ = Mean parental height + 7
Mid Parental Height (MPH) for ♀ = Mean parental height - 7
Target Centile Range (TCR) for ♂ = MPH ± 12
Target Centile Range (TCR) for ♀ = MPH ± 11

Instruments for Weight & Height Measurement

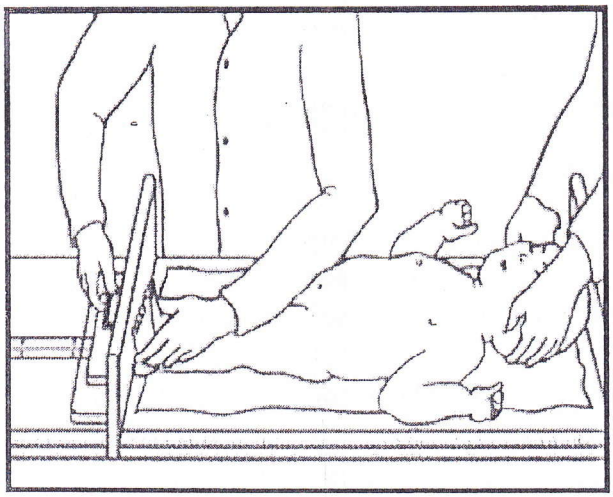




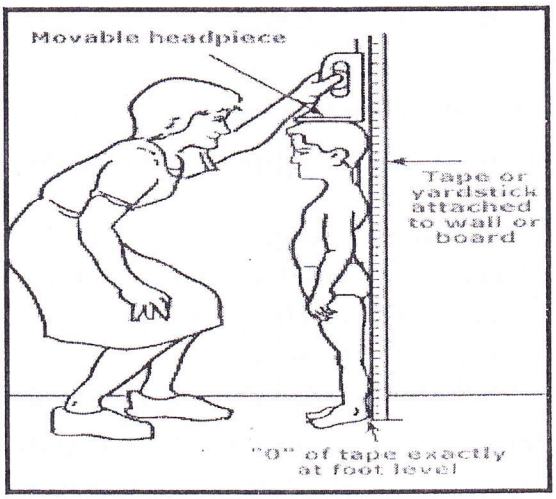


Weight is measured using a calibrated balance

- Infants should be naked
- Children should wear only underwear



Infantometer



Stadiometer

Length is measured using an infantometer
Height is measured using stadiometer

Etiology

A) Normal variants (80%)

	1. Familial (genetic)	2. Constitutional growth delay
Family history	Positive (parents are short)	Positive
Growth velocity	Normal	Period of transient decelerated growth
Bone age	Normal	Delayed
Puberty	Normal	Delayed
Adult height	Short adult height	Normal adult height
Treatment	GH may be useful	Reassurance

B) Pathological (20%)

1. **Endocrinal**
   - Hypothalamus: Laurance-Moon Biedl
   - Pituitary: Hypopituitarism
   - Thyroid: Congenital hypothyroidism
   - Suprarenal: Cushing, CAH
   - Gonads: Precocious puberty
   - Pancreas: DM
2. **Chronic debilitating diseases**
   - CVS: CHD, RHD
   - Resp.: TB, Cystic fibrosis, asthma
   - Renal: CRF, RTA, DI
   - GIT: Malabsorption, IBD
   - Immunodeficiency
   - Hepatic: Cirrhosis, Wilson's
   - Collagen: JRA
   - Blood: Chronic hemolytic anemia
   - Infection: TB, suppurative lung S.
   - Metabolic: aa, organic acidemias
3. **Chromosomal**
   - Turner
   - Down
   - Trisomy 18
4. **Congenital syndromes**
   - Prader-Willi
   - Silver-Russel
   - Cornelia De Lange (microcephaly,synophrys…)
   - Progeria
5. **Metabolic**
   - Aminoacidopathies
   - Organic acidemias
   - Storage diseases (Gaucher, NP...)
   - Minerals: Cu, Fe…
6. **Psychological (deprivation) dwarfism**
   - Disturbed child-mother or family relation → ↓↓ GH release (Unknown mechanism)
   - Growth will be resumed if the child is provided with love & care (i.e., Catch-up)
   - Bone age is delayed
7. **Malnutrition:** Malnutrition → ↓↓ Synthesis of GH mediators (Growth factors)
8. **Skeletal (=Causes of <u>Disproportionate</u> short stature)**
   - Rickets
   - Achondroplasia (<u>large head</u>, <u>short limbs</u>& <u>normal trunk</u>) + Normal mentality
   - Hypochondroplasia (normal head + Features are not prominent as achondroplasia)
   - Osteogenesis imperfecta (osteoporosis + multiple fractures + blue sclera + hearing ↓↓)
   - Mucopolysaccharidoses
   - Chondroectodermal dysplasia (short limbs + ectodermal dysplasia + polydactyly + CHD)
9. **Primordial short stature(LBW short stature)**
   - IUGR (Congenital infections, Congenital malformation, placental insufficiency)
   - Silver-Russel syndrome (triangular face, incurved 5th finger, hemihypertrophy)
   - Seckel syndrome (Bird-headed dwarfism)
10. **Drugs:** Steroids

Approach to a case of short stature

(A) History:

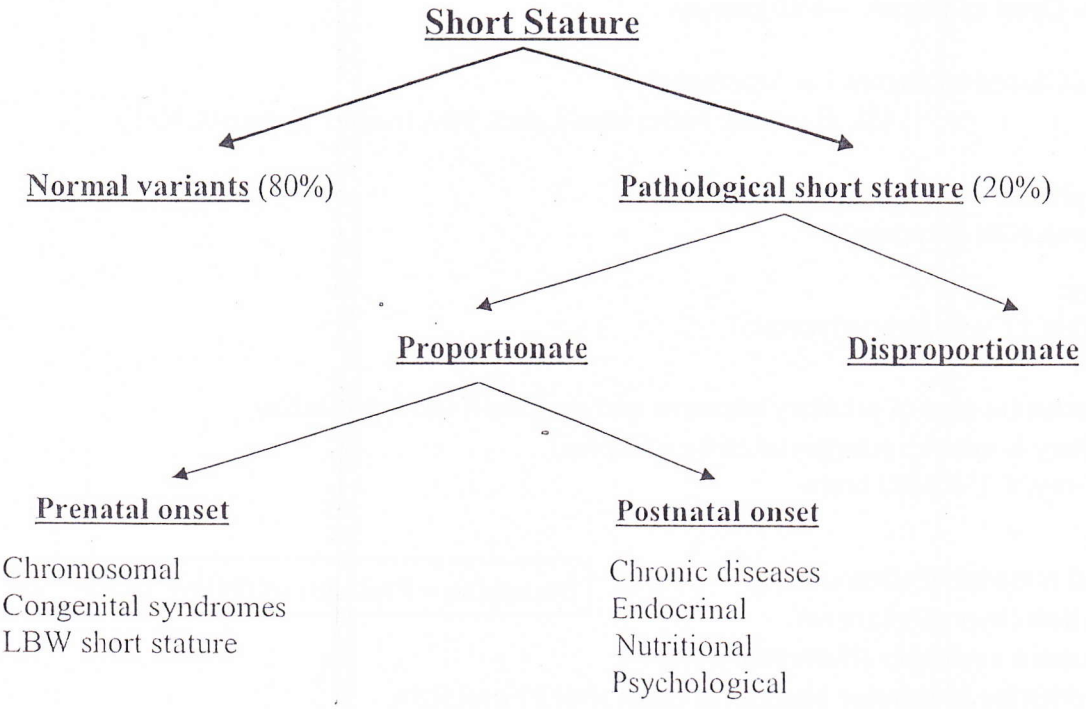
- Symptoms of different system affection
- Nutritional history
- Perinatal history: Birth length& weight, causes of IUGR
- Psychological assessment
- Parental heights & TCR

(B) Physical examination:

- Measure height/length, US& LS, arm span ⟶ Proportionate or disproportionate
- Manifestations of chromosomal abnormalities (e.g., Turner…), congenital syndromes (e.g., Prader-Willi), hypopituitarism (microphallus)
- Complete system examination.

(C) Investigations:

- CBC, ESR, UA, electrolytes, KFTs, LFTs
- Karyotyping is routine in **all ♀ with short stature**
- Bone age (Lt wrist X-ray): normal in familial cases& skeletal dysplasia
- Imaging: CT, MRI
- Investigations of endocrinal causes (start with thyroid): *See before*



Tall Stature

Definition

Height more than 2 SD above the mean height for age & sex or > 97th percentile.

Etiology

1. **Familial (genetic or constitutional)**
   - +Ve family history.
   - Normal bone age
   - Normal puberty
   - Tall adult height.
2. **Exogenous obesity** ⟹ -Advanced bone age
3. **Precocious puberty** ⟹ -Tall child height
4. **Hyperthyroidism** ⟹ -Normal adult height
5. **Marfan:** ↑↑ arm span, ↓↓ US/LS
6. **Homocystinuria:**
7. **Klinefelter (XXY)& XYY syndrome**
8. **McCune-Albright syndrome**
9. **Cerebral gigantism (Sotos syndrome):**
   - Growth rate: -At birth → Macrosomic -1-5 yrs: accelerated rate of growth
     - >5 yrs → Normal growth rate - Normal adult height
   - Physical: Large head, dolicocephaly, hypertelorism, prominent jaw, large hands & feet
   - Mental: MR
   - Sexual: Normal
   - ↑↑ Risk of malignancy (Wilms, liver)
   - Normal endocrinal studies.
10. **GH excess** → Open epiphyses → Gigantism
    → Closed epiphyses → Acromegaly
    (Skull, coarse facies hands, feet, jaw, tongue, kyphosis, IGT)

Etiology:

- ☒ Hyperplasia
- ☒ Adenoma (GH-secreting)

Investigations:

- ↑↑ GH (No ↓↓ with hyperglycemia)
- ↑↑ IGF-1
- ↑↑ Prolactin (in case of pituitary adenoma secreting both GH& prolactin)
- ↓↓ Pituitary hormones (compression by adenoma)
- Skull X-ray, CT & MRI brain

Treatment:

- **Surgical** removal of adenoma
- **Irradiation** (hypopituitarism)
- Somatostatin analogues ***(Octreotide)***
- **Bromocriptine** (dopamine agonist) in cases with ↑↑ prolactin
- GH receptors antagonist ***(Pegvisomant)***

Dopamine = Prolactin-inhibiting factor

Fetal overgrowth syndromes

1. IDM
2. Beckwith-Wiedemann $
3. Cerebral gigantism (Sotos)
4. IGF-II excess

Treatment of familial tall stature

♂ → Testosterone enanthate

♀ → Ethinyl estradiol

When: Predicted adult height >3 SD
Severe psychological impairment

Diabetes Insipidus

(Insipidus = Tasteless)

Physiology of ADH (ADH = arginine vasopressin)

☒ **Control of ADH secretion:**

- **Plasma osmolality:** ↑↑ Osmolality ⟶ ↑↑ Osmoreceptors ⟶ ↑↑ ADH release
- **Extracellular volume:** ↓↓ ECV ⟶ ↑↑ Baroreceptors ⟶ ↑↑ ADH release
- **Stress, pain, drugs** (nicotine).

☒ **Action of ADH:**

ADH binds to vasopressin type-2 receptors ***(V_2 R)*** in the collecting ducts ⟶↑↑ cAMP ⟶ movement of preformed aquaporin water channels ***(AQP-2)*** to apical membrane ⟶↑↑ water permeability ⟶↑↑ water movement to the ***hypertonic*** medullary interstitium ⟶↑↑ water reabsorption

Definition

Inability to produce concentrated urine due to:

- Defect in ADH ***secretion*** ⟶ Central DI
- Defect in ADH ***action*** ⟶ Nephrogenic DI

Etiology

Central DI	Nephrogenic DI
A) Hereditary: AD mutation of ADH gene	**A) Hereditary:** -XLR mutation of V_2R gene* -AR/AD mutation of ~~*AQP-2*~~ gene
B) Acquired: • Trauma • Tumors • Irradiation • Infection • Infiltration • Immune • Empty-sella syndrome	**B) Acquired:** • Obstructive uropathy • Interstitial nephritis • VUR • Chronic pyelonephritis • Sickle cell anemia • CRF • Cystic diseases • Nephrocalcinosis • Hypokalemia • Hypercalcemia
C) Drugs: Alcohol	**C) Drugs:** Amphotericin B Lithium Demeclocyclin
D) Idiopathic: (diagnosis of exclusion) Periodic F/U is required for at least 4 yrs as DI may precede brain tumors	
E) DIDMOAD (Wolfram Syndrome): DI, DM, Optic Atrophy& Deafness	

Serum Osmolality

- Serum osmolality = 2 Na + Glucose/18 + BUN/3
- Normally = 285-295 mOsm/Kg

Osmolality = 2Na+ Glucose/18 + BUN/3

Clinical picture

- Polyuria (>2 L/m^2/day) & polydipsia, satisfied with water not by milk.

(NB: Breast milk has a low Na content; infants receiving cow's milk are more liable to hypernatremic dehydration).

- Dehydration, bouts of high fever.
- FTT
- Irritability & seizures (↑↑ Na & its correction).
- Nocturia & Enuresis.
- Picture of the cause in acquired forms of central & nephrogenic DI.

Investigations

Diagnosis of DI is established if serum osmolality >300 mOsmol/Kg H_2O and urine osmolality <300 mOsmol/Kg H_2O

Diagnosis of DI is unlikely if serum osmolality < 270 mOsmol/Kg H_2O or urine osmolality > 600 mOsmol/Kg H_2O

1. **Urine:**
   - **Volume:** Polyuria up to 4-10 L/day
   - **Specific gravity:** Low < 1010
   - **Osmolality:** Low < 300 mOsmol/Kg H_2O
2. **Blood:**
   - **Na:** Normal or ↑↑
   - **Osmolality:** Normal or ↑↑ >300 mOsmol/Kg H_2O
3. **Vasopressin test:** To differentiate between central & nephrogenic DI using intranasal *Desmopressin* (DDAVP=Desamino-D-arginine vasopressin= Minirin)
   - ⟶ ↑↑ Urine osmolality (Central DI)
   - ⟶ No ↑↑ urine osmolality (Nephrogenic DI)
4. **Water deprivation test:** "If serum osmolality is 270-300 mOsmol/Kg". Fluids are withheld (3-5 hr) with periodic measurement of urine& blood osmolality, and then vasopressin is given as before. [Stop if BW ↓↓ >3 %]
5. **Vasopressin plasma level:** Low in central DI.
6. **Investigation of the cause:** ↓↓ K, ↑↑ Ca, KFTs, MRI brain.
7. **Renal US:** Hydroureter& Hydronephrosis "functional" (2 ry to persistent polyuria).

Treatment

1. **Adequate fluid intake:** free access to water.
2. **Adequate caloric intake& low Na content:** Breast milk & low Na formula.
3. **Rx of the cause.**

Central DI	Nephrogenic DI
Desmopressin (DDAVP=Desamino-D-arginine vasopressin= Minirin) *Nature:* synthetic analogue of ADH *Dose:* 10 µg intranasal qd. (IV, tablets) *Other uses:* Nocturnal enuresis Hemophilia A vWD Donors of cryoprecipitate Platelet dysfunction Portal hypertension Renal/liver biopsy	1. **Diuretic therapy** • *Hydrochlorothiazide:* 2-4 mg/kg/day • *Amiloride:* 0.3 mg/kg/day *Mechanism:* "paradoxical response" ↓↓ Na ⟶ ↑↑ PCT Na reabsorption ⟶ ↓↓ H_2O delivery to *defective* DCT 2. **Indomethacin therapy** (PGs inhibitor) *Dose:* 2 mg/kg/day *Mechanism:* PGs ⟶ ↓↓cAMP *Side effects:* GIT, renal impairment

Syndrome of Inappropriate ADH Secretion

Definition

Inappropriately high plasma level of ADH not inhibited by ↓↓ serum osmolality or ↑↑ intravascular volume.

Etiology

1. **Overtreatment of central DI***
2. **CNS:** Encephalitis, TB meningitis, brain abscess, brain tumors, head trauma, surgery, postictal period, Guillain-Barre syndrome
3. **Respiratory:** Pneumonia, cystic fibrosis, +Ve pressure ventilation, pneumothorax
4. **Tumors:** Thymus, lung, Ewing's sarcoma
5. **Drugs:** vincristine & carbamazepine

Clinical picture

1. **Picture of the cause**
2. **Plasma volume:** Normal or slightly ↑↑
3. **Asymptomatic:** If serum Na > 120mEq/L
4. **Water intoxication:** Anorexia, nausea, vomiting, confusion, seizures.

Investigations

1. ***Hyponatremia*** (<135 mEq/L), hypochloremia & ***hypouricemia***
2. Plasma osmolality < 280 mOsmol/Kg H_2O
3. Urine osmolality > 100 mOsmol/Kg H_2O (usually > plasma osmolality)
4. Urine specific gravity ↑↑
5. Urine Na > 25mEq/L

Treatment

1. Fluid restriction ($1L/m^2/d$)
2. Frusemide with Na supplementation
3. Hemodialysis ⟶ Removal of excess water & normalization of electrolytes
4. Demeclocyclin (creation of nephrogenic DI)

	Homocystinuria	Marfan syndrome
Etiology	Cystathionine synthase ↓↓	Defect in collagen fibers
Inheritance	AR	AD
Mentality	MR	Normal
Muculoskeletal	Arachnodactyly (2 Tests), Pectus excavatum, High arched palate, Kyphoscoliosis	The same + Hernias Pneumothorax
Bone density	Osteoporosis	Normal
Joints	Stiff	Lax
Cardiovascular	AR, MR	AR, MR, Aortic dissection
Ocular	Myopia Lens dislocation (Downwards)	Myopia Lens dislocation (Upwards)
Vascular thrombosis	↑↑ risk of thrombosis	No ↑↑ risk of thrombosis
Investigations	↑↑ Homocystine in urine	No ↑↑ Homocystine in urine
Treatment	Low methionine diet B6 & folic acid	Supportive

Puberty

Definition

It is the period of life during which the **endocrine** & **gametogenic** functions of the gonads have developed to the point where reproduction is possible [physical & sexual maturation]

Adolescence

It is the period of life during which child becomes an adult [Physical, sexual, psychological & social maturation].So, puberty is 1st part of adolescence.

Physiology of Puberty

Sex hormones = Testosterone & Estrogen

- **Prepubertal stage:**
  - Hypothalamo-hypophyseal-gonadal axis is dormant (upper neuronal inhibition)
  - ↑↑ Sensitivity of H-H-G axis to sex hormones
  - LH & sex hormones: undetectable
- **1-3 yrs before puberty:**
  - GnRH & LH *pulsatile* secretion start to occur first during sleep
  - Gradual ↑↑ in amplitude & frequency of GnRH & LH pulses
  - Adrenarche: ↑↑ adrenal androgens (responsible for pubic hair, acne, voice…)
- **During puberty:**
  - GnRH & LH *pulsatile* secretion occur at 90-120 min intervals
  - No more diurnal variation
  - In ♀, +Ve feedback effect of estrogen causing LH surge in midcycle (ovulation)

Age of Onset of Puberty *(Variable)*

♀ = 8-13 yrs ♂ = 9-14 yrs

Factors affecting the age of Onset of Puberty

1. Osseous maturation (bone age):

- The onset of puberty is more closely related to osseous maturation than to chronological age
- Estrogen is responsible for bone maturation & epiphyseal closure in both ♀& ♂

2. Genetic factors

3. Nutrition: Good nutrition ⟶ earlier puberty

4. Body build: Moderate obesity ⟶ earlier puberty, Morbid obesity ⟶ delayed puberty

5. Physical activity(energy balance): ♀ athletes (ballet dancers & swimmers) ⟶ delayed puberty

Physical changes of Puberty

☒ **Females:**

- First sign of puberty is **breast** enlargement
- Followed by ⟶ Pubic hair ⟶ Axillary hair ⟶ Menarche
- Average age of menarche in Egyptian ♀ is 12.5 yrs
- Less obvious changes: ↑↑ Ovaries, uterus, labia & thickening of vaginal mucosa

☒ **Males:**

- First sign of puberty is **testicular** enlargement (Prader orchidometer)
- Followed by ⟶ Thinning & pigmentation of the scrotum ⟶ ↑↑ Penis ⟶ Pubic hair ⟶ Axillary hair
- Less obvious changes: ↑↑epididymis, seminal vesicles, prostate & gynecomastia (65%)

- **Prader orchidometer (12-ellipsoids):** 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 25 ml
- **Testicular volume:** Preadolescence = 1-3 ml
- **Testicular length** (exclude epididymis): Preadolescence = 1.5-3 cm

Stages of Puberty (= Tanner staging)

☒ **Females:**

Stage	1. Pubic Hair	2. Breasts
1	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast & papilla elevated as small mound ↑↑ areolar diameter
3	Darker, start to curl	Breast & areola enlarged, no contour separation
4	Coarse, Curly, abundant, but amount less than adult	Areola and papilla form 2ry mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of general breast contour

3. **Axillary hair** (3 stages)
   - No
   - Appearance
   - Adult type

☒ **Males:**

Stage	1. Pubic Hair	2. Penis	3. Testes
1	Pre-adolescent	Pre-adolescent	Pre-adolescent
2	Sparse, lightly pigmented, at the base of the penis	Slight enlargement	Enlarged scrotum- Pink
3	Darker, start to curl	Longer	Larger
4	Coarse & Curly	Larger (glans & breadth)	Larger- Dark scrotum
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

4. **Axillary hair** (as in females)

Secondary Sex Characters

2ry Sex Ch.	Male	Female
Voice	Deep	High pitched
Hair distribution	Beard, frontal baldness, chest, pubic hair (triangle with apex up)	Less body hair, ↑↑ scalp hair, pubic hair (triangle with base up)
Body shape	Masculine	Fat distribution (**b**reast & **b**uttocks)
skeleton	Wide shoulders, Narrow hips	Narrow shoulders, wide hips
Libido	↑↑ Libido	↑↑ Libido

Growth

- **Definition:** Increase in the **size** & **number** of cells
- It can be assessed by measurements as Weight, Height (Length) & Skull circumference
- It is dependent on different factors at different ages:
  - Fetal: Fastest period of growth (*See factors affecting IU growth*)
  - Infancy: Nutrition (Substrate availability)
  - Childhood: Growth hormone (& Thyroxine)
  - Puberty: Sex hormones (& Growth hormone)

Pubertal growth spurt

It is divided into 3 phases:

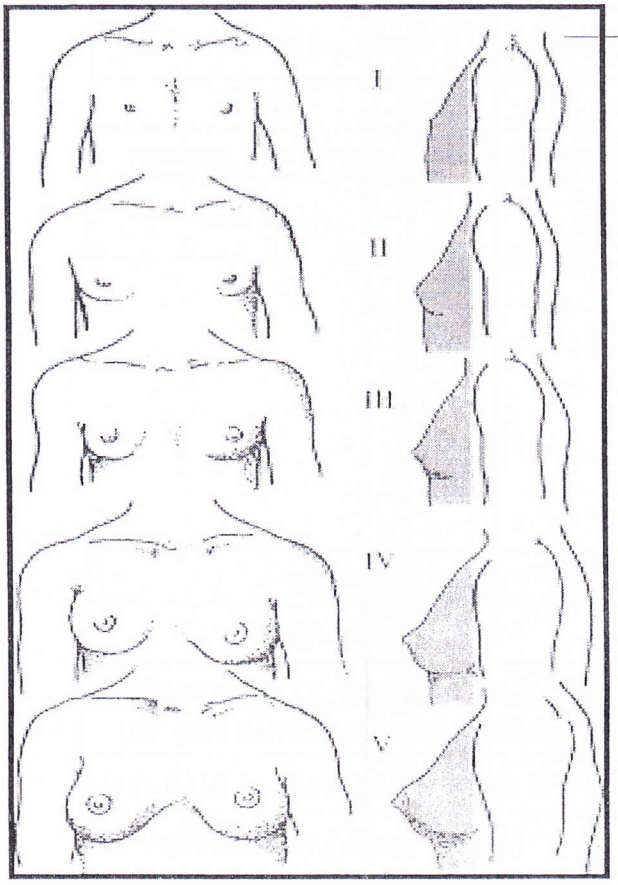
- Take-off = Minimum growth velocity
- Peak height velocity = Maximum growth velocity
- Decelerated phase

☒ **Females:**

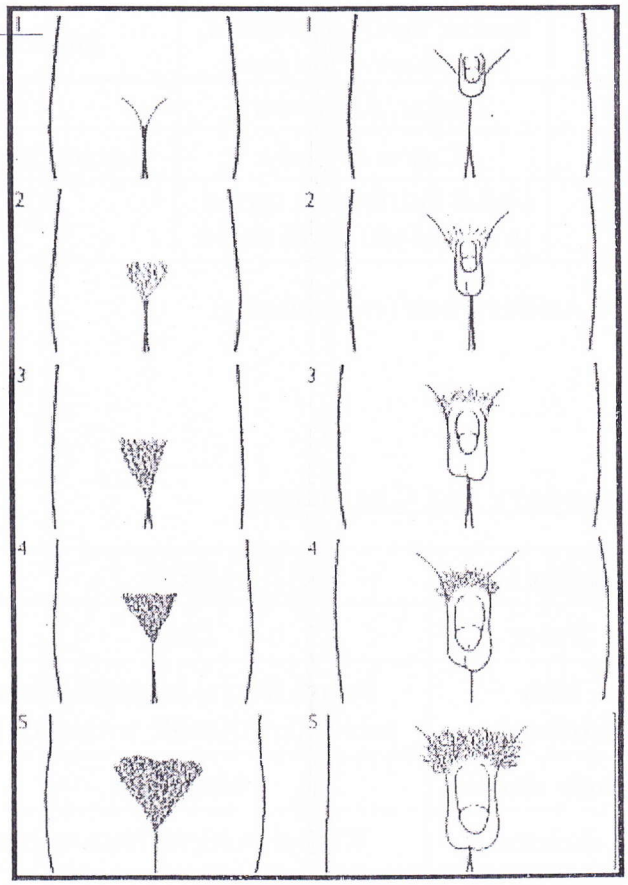
- Onset of peak height velocity = pubertal stage 2-3 [i.e., pre-menarcheal event]
- Height gain = 25 cm

☒ **Males:**

- Onset of peak height velocity = pubertal stage 3-4 [2 yrs after females]
- Height gain = 28 cm [Mean height difference between ♂ & ♀ = 13 cm, **why??**]



Tanner staging of female breast changes



Tanner staging of pubic hair

Precocious Puberty

Definition

The appearance of 2ry sexual characters before 8 yrs in ♀ and 9 yrs in ♂

	True Precocious Puberty	Precocious Pseudopuberty
Synonyms	Central (intra-cranial) Gonadotropin dependent	Peripheral (extra-cranial) Gonadotropin independent
H-H-G	Active	Inactive
FSH & LH	↑↑	↓↓
Gonads	Active	Inactive
Gametogenesis	Present	Absent
2ry sex characters	Isosexual لازم	Isosexual or heterosexual
GnRH stimulation	↑↑ LH & FSH	No ↑↑ LH & FSH

Precocious pseudopuberty ⟶ ↑↑ bone age ⟶ activation of HHG axis ⟶ True Precocious puberty (**Combined** Gonadotropin dependent **&** Gonadotropin independent Puberty)

Etiology

I) True Precocious Puberty:

A) Idiopathic (constitutional, functional)

B) Organic brain lesions

- Hypothalamic hamartoma
- Intracranial lesions
- Pineal region tumors

C) Radiotherapy

D) Hypothyroidism

True precocious puberty:
♀ ⟶ 80% of cases are idiopathic
♂ ⟶ 80% of cases are pathologic

II) Precocious Pseudopuberty:

		Gonadal	Adrenal	Exogenous
Female	**Isosexual (Feminizing)**	• McCune-Albright $ • Autonomous ovarian cyst • Ovarian tumors ➢ Granulose cell tumor ➢ Teratoma	Feminizing adrenal tumor	Estrogens
Female	**Heterosexual (Virilizing)**	•Ovarian tumors e.g., Androblastoma	• Virilizing adrenal tumor • CAH	Androgens
Male	**Isosexual (Virilizing)**	• Leydig cell tumor • Familial male precocious P.	• Virilizing adrenal tumor • CAH	Androgens
Male	**Heterosexual (Feminizing)**	• Sertoli cell tumor	Feminizing adrenal tumors	Estrogens

In ♂, **hCG secreting tumors** (Hepatoblastoma, CNS, mediastinum) ⟶ Isosexual precocious pseudopuberty

III) Incomplete Precocious Puberty:

- Premature thelarche
- Premature adrenarche
- Premature menarche

IV) Combined Puberty:

- Congenital adrenal hyperplasia
- McCune-Albright $
- Familial male precocious puberty

Leoprolide: synthetic long-acting GnRH agonist
- *Pulsatile* GnRH is needed to ↑↑ FSH & LH
- *Continuous* GnRH stimulation: suppression

True Precocious Puberty

Idiopathic (Constitutional, functional)

Incidence (♀: ♂= 5-10:1)
It is the cause of **PP** in 90% of ♀
It is the cause of **PP** in *only* 25- 75% of ♂

Etiology — True Isosexual
Sporadic (?? Familial)

Clinical picture *(Synchronous as normal)*

☒ **Females:**
Breast enlargement → Pubic hair → Axillary hair → Menarche (+2ry sex characters)

☒ **Males:**
Testicular ↑↑ → Thinning & pigmentation of the scrotum → Penis ↑↑ → Pubic hair → Axillary hair (+2ry sex characters)

☒ **Both ♀ & ♂:**
Tall as children, Short as adults
Gametogenesis: present(Pregnancy& N.emissions)
Mentality: compatible with chronologic age

☒ **Course:**
Progressive (rapidly or slowly) or regressive

Investigations
1. **Gonadotrpins (FSH & LH)**
   - ↑↑ FSH& LH with detected pulsatile LH
   - GnRH stimulation: Brisk response ↑↑
2. **Sex hormones:** ↑↑ (consistent with bone age)
3. **Bone age:** Advanced bone age
4. **CT, MRI brain:** to exclude I.C. lesions (♂)*
5. **Pelvic U/S:** ↑↑ Ovaries, uterus ± ovarian cysts

Treatment
GnRH analog *(Leoprolide)*: 0.25-0.3 mg/Kg IM every 4 wks (Other routes = intra nasal, SC)
Side effects: Recurrent sterile fluid collection at injection sites
Effects: ↓↓ GTH& sex hormones + ↓↓ growth rate to normal + ↑↑ adult height
Regression of 2 ry sex characters (breasts, menses, testicular size, pubic hair)

Organic Brain lesion

Incidence
It is the cause of **PP** in 10% of ♀
It is the cause of **PP** in 25- 75% of ♂

Etiology
1. **Hypothalamic hamartoma**
2. **Intracranial lesions** (involving the hypothalamus)
   - TB meningitis
   - Encephalitis
   - Tumors (astrocytoma, ependymoma…)
   - Trauma
   - Tuber sclerosis
   - Neurofibromatosis (optic glioma)
3. **Pineal region tumors** (germinoma, astrocytoma)

True Isosexual

Clinical picture
☒ **Endocrinal:** may precede the IC lesion
☒ **Picture of the cause:** ↑↑ ICT, visual field…
☒ **Hypothalamic syndrome:**
- Hypothermia, hyperthermia, adipsia, DI
- Obesity, cachexia
- Hypersomnia
- Gelastic seizures (unnatural laughing)

Investigations as in constitutional precocious P.
Treatment GnRH analog *(Leoprolide)*
Rx of the cause

PP following Radiotherapy

Mechanism
Radiotherapy → True Precocious Puberty

True Isosexual

Clinical picture
1. **Precocious puberty:** ↑↑ growth
2. **GH & TSH deficiency:** ↓↓ growth
3. **Net result:** Normal growth

Treatment
- GnRH analog (Leoprolide): 0.25-0.3mg/Kg IM every 4 wks
- GH & Thyroid supplementation

Hypothyroidism& precocious puberty

Incidence
Hypothyroidism usually cause delayed puberty*
Precocious puberty **may** occur in severe, untreated 1ry hypothyroidism of long duration

Mechanism & C/P
TSH & GTH (LH & FSH) have identical α-chain
↓↓ T_3, T_4 → ↑↑ TSH → ↑↑ FSH receptors →

☒ **Females:**
↑↑ Estrogen → ↑↑ Breast& Bleeding (menses)
No ovulation

Incomplete Isosexual True

☒ **Males:**
↑↑ Sertoli cells → ↑↑ Testicular size
No ↑↑ of Leydig cells → No ↑↑ testosterone
No virilization

Investigations
1. **TSH & prolactin:** ↑↑
2. **Gonadotrpins (FSH & LH):** ↓↓
3. **CT, MRI brain:** ↑↑ Sella
4. **Pelvic U/S:** Ovarian cysts

Treatment Thyroid supplementation (↓↓ TSH)

Precocious Pseudopuberty

Gonadotropin-Secreting Tumors	Familial male Precocious Puberty 1ry Leydig cell hyperplasia	McCune-Albright Syndrome
I) **Hepatoblastoma:** **Mechanism** ▪ It secretes hCG ⟶ ↑↑ LH receptors ⟶ ↑↑ Leydig cells ⟶ ↑↑ Testosterone ▪ No spermatogenesis **Clinical picture** (Only in ♂ ≈ 2 yrs) ▪ Isosexual precocious pseudopuberty ▪ Hepatomegaly **Investigations** ▪ **hCG & α-fetoprotein:** ↑↑ ▪ **Plasma testosrerone:** ↑↑ ▪ **Gonadotrpins (FSH & LH):** ↓↓ [In the past, ↑↑ LH due to cross reactivity with hCG] ▪ **Testicular biopsy:** Leydig cell hyperplasia ▪ **Bone age:** Advanced bone age II) **Other tumors:** ▪ **Type:** Teratoma, teratocarcinoma ▪ **Site:** CNS, mediastinum, gonads	**Etiology** (AD) **Mechanism** (Gonadotropin-independent) ▪ Activation mutation of LH receptors ⟶ ↑↑ Leydig cells⟶ ↑↑ testosterone ⟶ ↑↑ bone age ▪ No spermatogenesis **Clinical picture** (Only in ♂, 2 yrs) ▪ Isosexual precocious pseudopuberty ▪ True Isosexual precocious puberty may follow when bone age reaches pubertal age (combined) **Investigations** ▪ **Plasma testosrerone:** ↑↑ ▪ **Gonadotrpins (FSH & LH):** ↓↓ ▪ **Testicular biopsy:** Leydig cell hyperplasia ▪ **Bone age:** Advanced bone age **Treatment** ▪ Ketokonazole (# Testosterone synthesis) ▪ GnRH analog (Leoprolide): in true puberty	**Etiology** Autonomous hyperfunction of glands **Clinical picture** (Usually in ♀ ≈ 3 yrs) I) **Skin:** Pigmentation (Café-au-lait patches) II) **Skeletal:** Fibrous dysplasia III) **Endocrinal:** 1. **Gonads** ⟶ Precocious pseudopuberty [Functioning follicular cyst ⟶ ↑↑ Estrogen] True Isosexual precocious puberty may follow when bone age reaches pubertal age (combined) 2. **Thyroid** ⟶ Hyperthyroidism 3. **Adrenal** ⟶ Cushing syndrome 4. **Pituitary** ⟶ GH excess (gigantism or acromegaly) **Treatment** ☒ **Functioning ovarian cyst:** ▪ Surgery or aspiration ▪ Aromatase inhibitor *(Testolactone)* ▪ Anti-estrogen *(Tamoxifen)* ▪ GnRH analog (Leoprolide): (When??) ☒ **Hyperthyroidism** ☒ **Cushing** ☒ **GH excess:** *Octreotide*

Incomplete Precocious Puberty (Partial)

Definition

Isolated precocity of one of the 2 ry sexual characters before 8 yrs in ♀ and 9 yrs in ♂ without development of other signs of puberty. It is usually **transient**

Premature Thelarche	Premature Pubarche (Adrenarche)	Premature Menarche
Definition Isolated **breast** development **Etiology** Sporadic (? Familial) **Clinical picture** ▪Age of onset: During the 1st 2 yrs. May at birth ▪Course: Transient (3-5 yrs) Rarely progressive ▪Bilateral or unilateral ▪**Atypical (exagerated) thelarche** ↑↑ bone age, U/S ⟶ ↑↑ Ovaries **Investigations** ▪FSH, LH, Estrogen: Normal ▪Bone age: ± Advanced bone age ▪Pelvic U/S: ± Ovarian cysts **Treatment** Benign but F/U is needed as it may be 1st sign of precocious puberty	**Definition** Isolated appearance of **sexual hair** **Etiology** Premature ↑↑ adrenal androgens **Clinical picture** (♀ > ♂) ▪Sexual hair: pubic & axillary hair ▪ **Atypical premature adrenarche:** Systemic androgenic effects (acne, ↑↑ bone age…) ▪Course: Transient **Investigations** ▪FSH, LH, sex hormones: Normal ▪DHEA: ↑↑ ▪Bone age: ± Advanced bone age **Treatment** Benign but F/U is needed as it may be 1st sign of precocious puberty	**Definition** Isolated **menses** **Clinical picture** ▪1-3 attacks of menstrual bleeding ▪Course: Transient **Investigations** ▪FSH, LH, Estrogen: Normal ▪Pelvic U/S: ± Ovarian cysts **Treatment** Benign but F/U … **DD** (Vaginal bleeding) **1.** Child abuse **2.** FB **3.** Vulvo-vaginitis **4.** Uterine sarcoma

Precocious puberty in ♂:

A) True precocious puberty

B) Precocious pseudopuberty

1. Isosexual

- Gonadal: Leydig cell tumor, familial male precocious puberty
- Adrenal: Virilizing adrenal tumor & CAH
- Exogenous: Androgen
- Gonadotropin-secreting tumors

2. Heterosexual

- Gonadal: Sertoli-cell tumor
- Adrenal: Feminizing adrenal tumor
- Exogenous:Estrogen

C) Incomplete Precocious puberty

Premature adrenarche

D) Combined Precocious puberty

- Familial male precocious puberty
- CAH

Precocious puberty in ♀:

A) True precocious puberty

B) Precocious pseudopuberty

1. Isosexual

- Gonadal: McCune-Albright $

Autonomous ovarian cyst, ovarian tumors

- Adrenal: Feminizing adrenal tumor
- Exogenous: Estrogen

2. Heterosexual

- Gonadal: ovarian tumors
- Adrenal: Virilizing adrenal tumor& CAH
- Exogenous: Androgen

C) Incomplete Precocious puberty

Premature thelarche, Adrenarche, menarche

D) Combined Precocious puberty

- McCune-Albright $
- CAH

Adrenal Glands

A) Adrenal cortex	B) Adrenal medulla
1. **Zona Gomerulosa** ⟶ Mineralocorticoids • Aldosterone • Deoxycorticosterone (DOC) "Weak…" 2. **Zona Fasiculata** ⟶ Glucocorticoids • Cortisol (10 mg/m^2/d) } *17(OH) corticosteroids* • Corticosterone 3. **Zona Reticularis** ⟶ Androgens • DHEA } *17-Ketosteroids* (urine) • Androstenedione	***Products:*** Catecholamines 1. Adrenaline 2. Noradrenaline } *Vanillylmandelic acid* (VMA) 3. Dopamine Urinary VMA ↑↑ in: • Pheochromocytoma • Neuroblastoma • Vanilla-containing foods

Mineralocorticoids

☒ **Control of secretion:**
- **Renin-angiotensin system:** ↓↓ ECV & ↓↓ Renal perfusion, ↓↓ GFR
- ↑↑ **Serum K** ⟶ ↑↑ Aldosterone
- **ACTH** (Minor role)

☒ **Action:**
- ↑↑ Na & H_2O reabsorption
- ↑↑ K & H^+ secretion

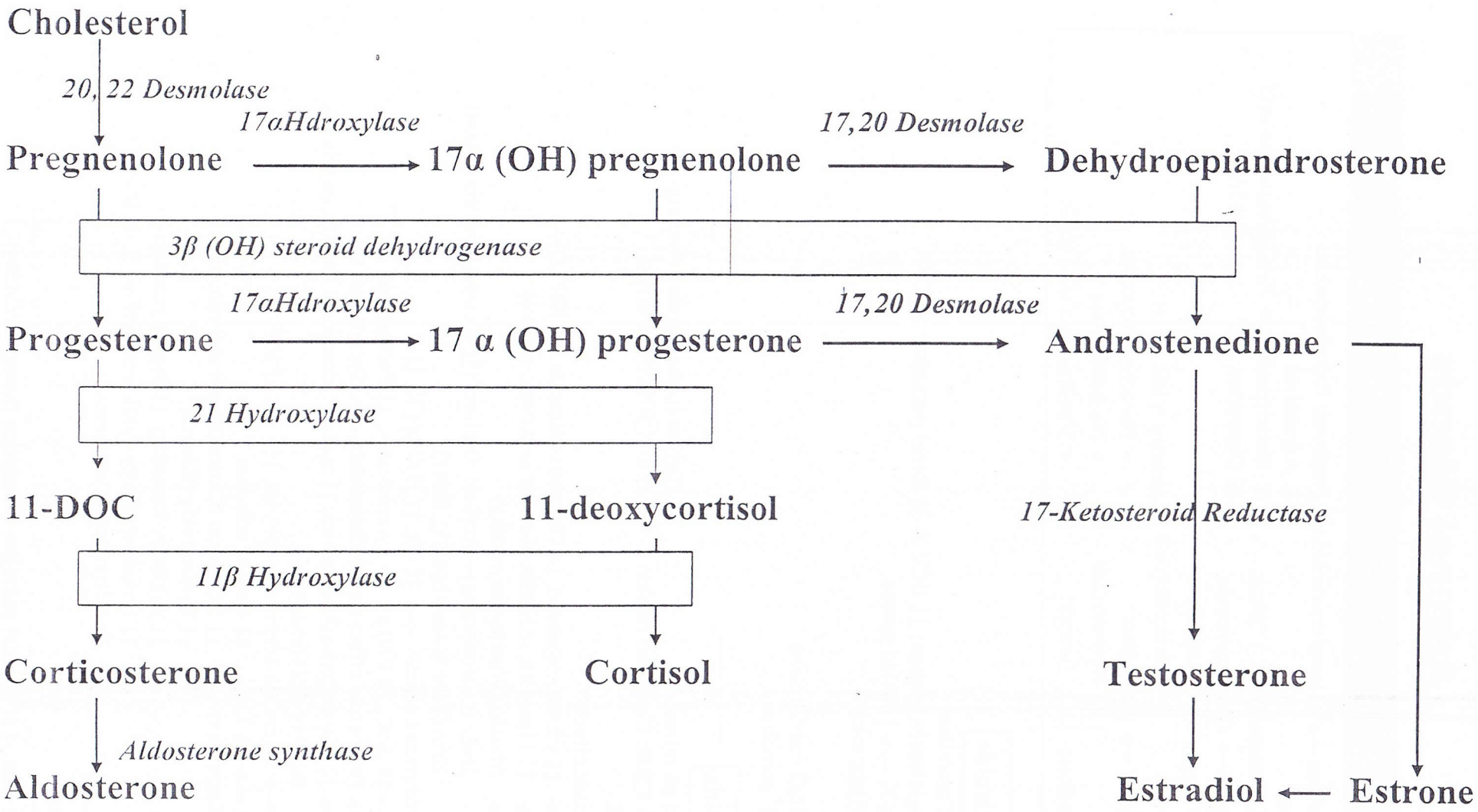
Glucocorticoids

☒ **Control of secretion:**
- **ACTH & CRH:** Circadian rhythm { Highest in the morning (waking-up); ↓↓ to < 50% by midnight
- **Feedback**

☒ **Action & side effects:**
- CHO ⟶ ↑↑ Gluconeogenesis, ↓↓ Glucose utilization (3), IGT, DM
- Fats ⟶ ↑↑ Lipolysis, redistribution (Facio-cervico-trunkal)
- Ptn ⟶ Muscle (Wasting, myopathy)
  Bone (Osteoporosis) – Anti-vit. D effect (↓↓ Ca intestinal absorption)
  Skin (Poor wound healing, striae)
- Mineralocorticoid effect ⟶ ↑↑ Na, ↑↑ H_2O, ↓↓ K, ↓↓ H^+
- Blood ⟶ ↑↑ RBC, ↑↑ PNLs + ↓↓ Lymphocytes, ↓↓ Eosinophils
- CVS ⟶ Permissive effect on catecholamines ⟶ Hypertension
- CNS ⟶ ↓↓ Brain edema (Vasogenic), ↑↑ appetite, emotional lability, psychosis, memory disturbance
- Growth ⟶ Direct inhibition of epiphyses, ↓↓ GH, ↓↓ IGF-1
- Immune ⟶ ↓↓ TH_1 ↑↑ Risk of infection
- Anti-inflammatory ⟶ ↓↓ Migration (Chemotaxis & diapedesis)
  ↓↓ Permeability (Edema)
  ↓↓ Antibody formation, ↓↓ Ag/Ab reaction
  ↓↓ Proinflammatory cytokines (TNF-α, IL-1, IL-6)
  Stabilization of lysosomes

Androgens

☒ Under the control of cortical androgen stimulating hormone (CASH)
☒ Growth promoting effect & androgenic effects


Cholesterol
20, 22 Desmolase
17αHdroxylase
17,20 Desmolase
Pregnenolone
17α (OH) pregnenolone
Dehydroepiandrosterone
3β (OH) steroid dehydrogenase
17αHdroxylase
17,20 Desmolase
Progesterone
17 α (OH) progesterone
Androstenedione
21 Hydroxylase
11-DOC
11-deoxycortisol
17-Ketosteroid Reductase
11β Hydroxylase
Corticosterone
Cortisol
Testosterone
Aldosterone synthase
Aldosterone
Estradiol
Estrone

Congenital Adrenal Hyperplasia

Definition

AR disorders of cortisol biosynthesis ⟶ ↑↑ ACTH ⟶ adrenocortical hyperplasia ⟶ ↑↑ production of intermediate metabolites ⟶ Variable C/P (Virilization, HTN, salt loss…)

Classification

Type (Enzyme)	Biochemical Defects	C/P	Investigations
-Hydroxylase deficiency **90% of all cases** . Classic ▪ **Simple virilizing** ▪ **Salt losing** . **Non-classic:** ıte onset .ess severe Hirsutism in peripubertal ♀	Progesterone ↓ 11-DOC 17α Progesterone ↓ 11-Deoxycortisol	**A) Simple virilizing:** ♂: • Normal at birth • Isosexual precocious pseudopuberty (at 6 months) • 2 ry sex characters (Penis, scrotum, pubic hair, deep voice, ↑↑ bone age, musculinization) ♀: • Ambiguous genitalia • XX-intersex • Clitoromegaly, labial fusion, labial pigmentation • Heterosexual precocious pseudopuberty • ♂ 2 ry sex characters **B) Salt-losing:** Virilization + Salt losing manifestations: (FTT, vomiting, dehydration, hypotension, shock, acidosis, RD, cyanosis)	↓↓ **Na**, ↑↑ **K**, ↑↑ H^+ (acidosis) ↓↓ **Glucose** ↑↑ PRA ↑↑ **17(OH)Prog.** ↓↓ Cortisol ↓↓ Aldosterone ↑↑ DHEA ↑↑ U.Ketosteroid ↑↑ Bone age US
1 **β-Hydroxylase deficiency** . **Classic** **Non-classic:** milder	**11-DOC** ↓ Corticosterone	**A) Virilization:** as before **B) Hypertension:** (11-DOC)	↑↑ DOC ↓↓ **K** ↓↓ PRA
3 **β-(OH) Steroid eydrogenase deficiency**	Pregnenolone ↓ Progesterone	**A) Salt losing:** … **B)** ♂: Incomplete virilization **C)** ♀: Mild virilization	
),22 Desmolase deficiency .ipoid adrenal hyperplasia	Cholesterol ↓ Prognenolone	**A) Salt losing:** … **B)** ♂: Phenotypic female **C)** ♀: Normal (No puberty)	
1-α-Hydroxylase deficiency	Pregnenolone ⟶ Pregesterone ⟶	**A) HTN** **B)** ♂: Phenotypic♀ Or incomplete virilization **C)** ♀: Normal (No puberty)	↑↑ DOC ↓↓ K ↓↓ PRA
1 **20 Desmolase deficiency**	17(OH)Pregnenolone⟶ 17(OH)Pregesterone ⟶	**A) HTN** **B)** ♂: Phenotypic♀ Or incomplete virilization **C)** ♀: Normal (No puberty)	

Virilization: 1, 2 **HTN:** 2, 5 **Salt losing:** 1, 3, 4

Disease	Treatment
21-Hydroxylase deficiency (0.1)	**A) Glucocorticoids& Mineralocorticoids:** **a. Hydrocortisone** • 10-15 mg/m^2/day divided / 8 hrs • Doubled or tripled during periods of stress or infection **b. 9-α fludrocortisol** (Astonin H or cortilone) • 0.05-0.2 mg/day oral **c. Monitoring of adequacy:** ➢ **Clinical** improvement (hypotension), ↓↓ pigmentation ➢ **Laboratory:** ↓↓ PRA, normal electrolytes, 17 (OH) progesterone, DHEA level **B) Surgical** • Clitoris Resection • Vaginoplasty **C) Antenatal diagnosis:** Chorionic villous sample (Sex & Genetic) **D) Antenatal Treatment:** of **affected female** fetus • Dexamethasone (20 µg / Kg of maternal weight) should be started at 6th gestational week • Continue **only** in cases of affected female fetus (CVS)
11-β-Hydroxylase deficiency	**a. Hydrocortisone** **b. Anti-hypertensives**
3-β-(OH) Steroid deydrogenase deficiency	**a. Hydrocortisone** **b. Fludrocortisone** **c. Testosterone:** in incompletely virilized ♂
20,22 Desmolase deficiency = Lipoid adrenal hyperplasia	**a. Hydrocortisone** **b. Fludrocortisone** **c. Estrogens for both** ♂ & ♀
17-α-Hydroxylase deficiency & 17, 20 Desmolase deficiency	**a. Hydrocortisone** **b. Anti-hypertensives** **c.** ♀: Estrogens **d.** ♂: Estrogens or Testosterone (according to external genitalia)

- **Intersex** (Hermaphroditism): Discrepancy between the morphology of gonads & external genitalia. The new proposed term is disorders of sex development (DSD)
- **Ambiguous genitalia**: Sex cannot be identified from external genitalia **(Atypical genitalia)**
- **Virilized female**: Clitoromegaly, labial fusion, labial pigmentation
- **Incompletely virilized male**: Small phallus, small ± undescended testes, bifid scrotum, hypospadias
- **Microphallus**: Penile size < 5th for age: neonate with stretched penile length < 2 cm

Adrenocortical Insufficiency

Definition

- Deficient production of cortisol &/or aldosterone or their action
- **Addison disease:** Acquired primary adrenal insufficiency

Etiology

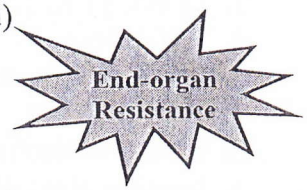
(A) Primary:

1. Adrenal aplasia or hypoplasia (X-Linked)
May be associated with Duchenne muscular dystrophy, mental retardation Or
Hypogonadotropic-hypogonadism (↓↓ GnRH) "DAX-1" mutation

2. Familial glucocorticoid deficiency
- Isolated glucocorticoid deficiency (ACTH receptor defect) or as a part of
- Triple A syndrome: Alacrima- Achalasia- ACTH unresposiveness

3. Congenital adrenal hyperplasia (Impaired steroidogenesis)
- 20,22 Desmolase
- 21-Hydroxylase
- 3β (OH)steroid dehydrogenase
- Aldosterone synthase (isolated)

4. Pseudohypoaldosternism (End organ resistance)
Treated with supplementary salt (Mineralocorticoids are **ineffective**)



5. Adrenoleukodystrophy (X-Linked)
- Peroxisomal disease ⟶ accumulation of very long chain FA (VLCFA) ⟶
  - Adrenal gland ⟶ Insufficiency [Childhood (XL) or Neonatal (AR)]
  - White mater ⟶ Academic deterioration, behavioral changes, dysarthria, dysphagia, visual disturbances, seizures, spasticity, ataxia.
- Addison disease may precede neurological manifestations by many years

6. Mitochondrial diseases
Kearns-Sayer $ (KSS)

7. Cholesterol related disorders
- Wolman disease: Lysosomal acid lipase deficiency ⟶ accumulation of cholesterol esters (HSM, steatorrhea)
- Smith-Lemli-Opitz syndrome (SLOS): Microcephaly, ptosis, ambiguous genitalia

8. Immune:
- Isolated
- Type I autoimmune polyendocrinopathy "HAM" (Hypoparathyroidism, Addison, Mucocutaneous candidasis)
- Type II autoimmune polyendocrinopathy (Thyroid, IDDM)

9. Infection
- TB
- Meningococcemia (Warehouse-Friderichsen)

10. Neonatal adrenal hemorrhage
- Birth injury
- Asphyxia

11. Iatrogenic
- Surgical removal
- Drugs: Ketokonazole, mitotane

(B) Secondary:

1. **ACTH or CRH deficiency:** Isolated or multiple, pituitary or hypothalamic (I I I I I I E)
2. **Abrupt cassation of steroid or ACTH therapy** (Large dose + Long duration)??
3. **Fetal adrenal gland suppression** (Maternal Cushing or steroid therapy)

Clinical picture

(A) Acute suprarenal failure (Crisis): (as in cases of CAH, adrenal hemorrhage, Warehouse-Friderichsen syndrome, Addisonian crisis)

- Vomiting, abdominal pain, asthenia
- Dehydration, shock (poor peripheral perfusion, hypotension & acidosis)
- Hypotonia, coma, seizures (↓↓ Na, ↓↓ glucose)

Precipitating factors: Infection, trauma, fatigue, surgery

(B) Gradual onset of:

- Asthenia, anorexia, abdominal pain, weight loss, FTT, hypotension
- Salt craving
- Pigmentation: Face, neck, axilla, nipple, areola, genitalia, pressure areas (absent in secondary causes, Why?)

Investigations

A) Laboratory:

1. ↓↓ Na, ↑↑ K, ↑↑ H^+ (Metabolic acidosis)
2. ↓↓ Glucose
3. Plasma renin activity (PRA)↑↑
4. Urinary Na ↑↑
5. CBC ⟶ Neutropenia, lymphocytosis, eosinphilia
6. Investigations of the cause: Serum VLCFA, Anti-adrenal antibodies

B) Hormonal:

1. Plasma cortisol *(before & after* ACTH administration*)*: ↓↓ (N = 5-25 µg/dL) **Most Definitive**
2. Plasma ACTH
   - ↑↑ in primary causes
   - ↓↓ in secondary causes
3. ACTH stimulation test (Synacten IM daily for 3 days) ⟶
   Plasma cortisol ↑↑ only in secondary causes
4. Plasma Aldosterone
5. Steroid precursors (DHEA, DHEA-S, androstenedione, testosterone, PRA, 17(OH) progesterone, 11-deoxycortisol)

C) Imaging:

1. ECG: Hyperkalemia
2. Abdominal US: Calcification
3. CT & MRI

ECG changes in ↑↑ K
1. ↑↑ PR interval
2. Wide QRS
3. Tall peaked T wave**
4. VF
5. Cardiac arrest

Treatment

- *Once the diagnosis of acute suprarenal failure is suspected, immediate treatment should be started without waiting laboratory confirmation (rapidly fatal condition)*
- *Shock in acute suprarenal failure is not responsive to volume expansion& catecholamines unless glucocorticoids are used simultaneously*

- **No need** for mineralocorticoids in familial glucocorticoid deficiency & 2 ry causes
- **No need** for glucocorticoids in isolated aldosterone deficiency & psudohypoaldosteronism
- Adrenal hemorrhage ⟶ Vitamin K, C Blood transfusion
- Autoimmune ⟶ exclude other immune and endocrinal disease

Surface area = $\frac{4 \times BW + 7}{BW + 90}$

I. Management of Acute suprarenal failure (crisis):

A) Fluid replacement:

- ***Volume***: 2500-3000 ml/m^2/day *(Shock + Deficit + Maintenance)*
- ***Rate***: 1/4 → First 2 hours, the **remaining** is divided into:
  - 1/2 → Next 8 hours
  - 1/2 → Next 14 hours
- ***Type***:
  - Blood glucose < 80 → G 10%: NS 1:1 or (G5%: NS = 2:1)
  - Blood glucose > 80 → G 5%: NS 1:1
- If the patient is shocked → Anti shock 20 ml/Kg (NS) over 30 min (subtracted)

B) Steroid replacement:

- **Hydrocortisone IV:**
  Bolus: small children 50 mg
  Large children 100-150 mg
  Maintenance: 100 mg/m^2/day divided / 6 hrs
  Then taper by decreasing the dose by 1/3 daily to reach the maintenance dose within 5 days
- **9-α fludrocortisol** (Astonin H or cortilone):
  Dose: 0.05-0.2 mg/day oral
  Indications: Severe salt losing manifestations

II. Maintenance therapy:

A) Hydrocortisone

- 10-15 mg/m^2/day divided / 8 hrs
- Doubled or tripled during periods of stress or infection

B) 9-α fludrocortisol (Astonin H or cortilone)

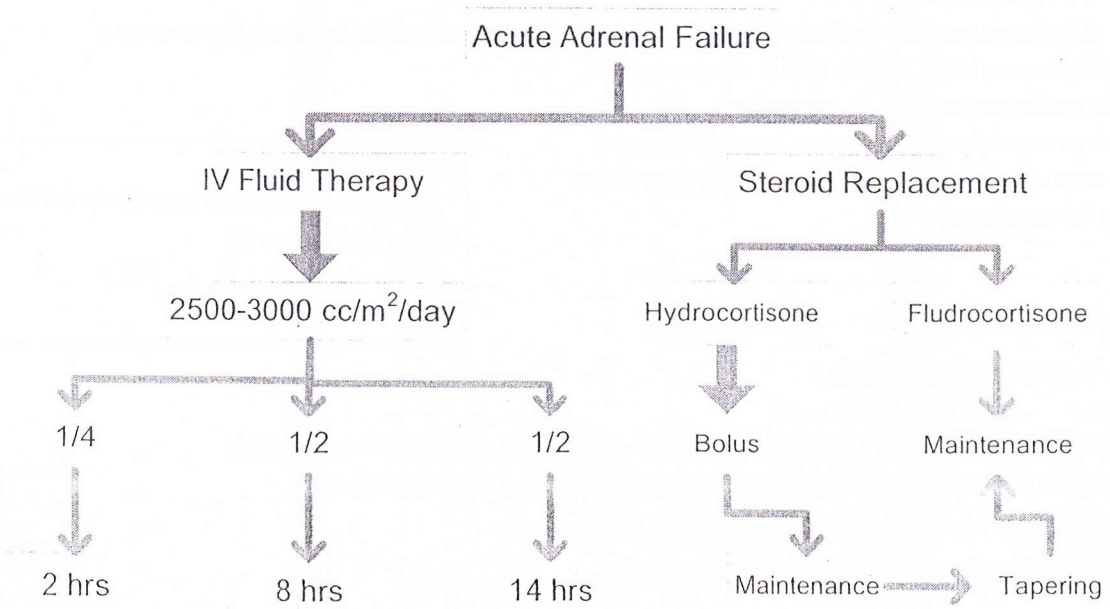
- 0.05-0.2 mg/day oral

Monitoring of adequacy:

- **Clinical** improvement (hypotension), ↓↓ pigmentation
- **Laboratory:** ↓↓ PRA, normal electrolytes, 17 (OH) progesterone, DHEA level

III. Treatment during surgery:

- Hydrocortisone IV 100 mg at the onset of anesthesia then 50 mg/ 6 hrs
- 9α fludrocortisol is given at night before operation



Hyperaldosteronism

Definition

Increased level of Aldosterone

Etiology

A) **Primary hyperaldosteronism(Conn's):** [hypertension - hypokalemia - ↓↓ PRA]
- Adrenal adenoma
- Adrenal hyperplasia
- Glucocorticoid-suppressible hyperaldosteronism (AD):
  - Aldosterone secretion is regulated by ACTH ⟶ Hypertension
  - Dramatic response to glucocorticoids (Dexamethasone)

B) **Secondary hyperaldosteronism:** [No hypertension - ↑↑ PRA]
- ↓↓ Effective plasma volume: Nephrotic $, Liver cirrhosis, Heart failure
- ↓↓ Renal perfusion: Renal artery stenosis
- Bartter & Gitelman syndromes

C) **Pseudohypoaldosternism** (End organ resistance) [Salt losing manifestations]

D) **Syndrome of apparent mineralocorticoid excess** (Pseudohyperaldosternism):
It is due deficiency of *11β (OH) steroid dehydrogenase* which converts cortisol to cortisone ⟶ ↑↑ Cortisol ⟶ ↑↑ mineralocorticoid receptors ⟶ Aldosterone like action ⟶ Hypertension, hypokalemia (***NB:*** Licorice also # this enzyme)

Clinical picture

A) **Primary hyperaldosteronism:**
- Hypertension: asymptomatic, headache, epistaxis, visual disturbances, heart failure, hypertensive encephalopathy (headache, vomiting, visual, coma, convulsions, ataxia)
- Hypokalemia: Polyuria, polydipsia, muscle weakness, paralysis, constipation & tetany

B) **Secondary hyperaldosteronism:** Picture of the cause

C) **Pseudohypoaldosternism:** Salt losing manifestations

D) **Pseudohyperaldosternism:** Hypertension, hypokalemia

Investigations

Laboratory: ↑↑ Na, ↓↓ K, ↓↓H^+ (metabolic alkalosis), ↓↓ PRA

Hormonal: ↑↑ Aldosrerne

Dexamethasone suppression test: Glucocortic suppressible hyperaldosteronism

Imaging: Abdominal US, CT & MRI: adenoma

Adrenal vein catheterization & sampling:

↑↑ Aldosrerne in one adrenal vein ⟶ Adenoma

↑↑ Aldosrerne in two adrenal veins ⟶ Hyperplasia

Exploratory labarotomy

Liddle syndrome:
Defect: Activation mutation of Na epithelial channels
C/P: HTN, ↓↓ K, ↓↓ PRA
Rx: HTN & ↓↓ K

Treatment

A) **Primary hyperaldosteronism:**
- Adenoma ⟶ surgical removal
- Hyperplasia ⟶ medical (spironolactone or amiloride), if failed ⟶ Surgery
- Glucocorticoid-suppressible hyperaldosteronism ⟶ Dexamethasone

B) **Secondary hyperaldosteronism:** Treatment of the cause

C) **Pseudohypoaldosternism:** Supplementary salt

Cushing Syndrome

Definition

Increased level of cortisol with **hypertension** and characteristic pattern of **obesity**

Etiology

A) Exogenous Cushing Syndrome (Cushinoid Syndrome)*:

Prolonged therapy with:

- ACTH
- Steroid

B) Endogenous Cushing Syndrome:

☒ **ACTH dependent:**

a. **Cushing disease:** ACTH secreting pituitary adenoma (microadenoma)
⟶ Bilateral adrenal hyperplasia (most common in children > 7 yrs)

b. **Ectopic ACTH:** Pancreatic islet cell carcinoma, neuroblastoma, Wilms tumor

☒ **ACTH-independent (adrenal):**

a. **Functioning adrenocortical tumor:** in infancy (Malignant* or benign)
b. **Primary pigmented nodular adrenocortical disease:** multiple, small pigmented nodules
c. **McCune-Albright syndrome** (autonomous hyperfunction)
d. **Multiple Endocrine Neoplasia (MEN) type I**

Clinical picture

- Characteristic obesity: Moon face, flushed plethoric face, doubled chin, trunkal, buffalo hump, thin limbs, striae rubra (abdomen& thigh).
- Delayed healing of wounds
- Osteoporosis ⟶ pathologic fractures and kyphosis
- Muscle weakness & myopathy
- Hyperglycemia
- Short stature
- Increased susceptibility to infection

- Hypertension ⟶ Heart failure
- Hypokalemia ⟶ Polyuria, polydipsia, muscle weakness, paralysis, constipation & tetany

- Androgen excess ⟶ Hirsutism, acne, deep voice, accelerated growth & clitoromegaly
- Adolescent female ⟶ Amenorrhea & hirsutism

Investigations

A) Diagnosis of Cushing Syndrome:

Laboratory:

- ↑↑ Na, ↓↓ K, ↓↓ H^+ (metabolic alkalosis)
- ↑↑ Glucose, OGTT
- CBC ⟶ ↑↑ RBC, ↑↑ PNLs, ↓↓ Lymphocytes, ↓↓ eosinophils

Hormonal:

- Cortisol level: loss of circadian rhythm then persistent elevation
- ↑↑ Salivary cortisol level (screaning)
- ↑↑ Urinary cortisol & 17(OH) corticosteroids
- Single dose dexamethasone suppression test (25 µg/Kg) ⟶ No ↓↓ in Cortisol level

B) Diagnosis of the etiology of Cushing syndrome:

- **Hormonal:**
  - Plasma **ACTH**
    - **a.** ACTH dependent → ↑↑ ACTH
    - **b.** Non-ACTH dependent → ↓↓ ACTH
  - **CRH** stimulation test:
    - **a.** ACTH dependent → ↑↑ ACTH & cortisol
    - **b.** Non-ACTH dependent → No response (Pituitary is suppressed)
  - **Dexamethasone** suppression test [D_1 30 µg/Kg/day qid, D_2 120 µg/Kg/day qid]
    - **a.** ACTH dependent → ↓↓ Cortisol
    - **b.** Non-ACTH dependent → No response

- **Imaging:**
  - **X-ray:** Osteoporosis, advanced bone age, ↓↓ thymic shadow
  - **Brain CT, MRI:** Pituitary microadenoma
  - **Abdominal US, CT, MRI:** adrenal adenoma

Treatment

1. **Adrenal tumors:** surgical removal
   - **a.** Benign → Subtotal adrenalectomy
   - **b.** Malignant → Total adrenalectomy

   ] + Replacement therapy (Cortisol & ACTH)
2. **Pituitary adenoma (Cushing disease):**
   - **a.** Pituitary irradiation (?? Hypopituitarism)
   - **b.** Surgical removal (Transphenoidal approach)
   - **c.** Total adrenalectomy: may be followed by the development of locally invasive pituitary tumor → ↑↑ ACTH → Hyperpigmentation *(= **Nelson syndrome**)*
   - **d.** Cyproheptadine (Centrally acting serotonin antagonist → # ACTH release)

Obesity & Overweight

Definition

- Obesity: BMI > 95th% for age& sex. (In adults BMI>30 Kg/m^2)
- Overweight: BMI = 85-95th% for age& sex
- Body mass index (BMI) = Weight (Kg)/ Height^2 (meters)
- BMI also ↑↑ in body builders due to ↑↑ muscle bulk
- More than 22 millions children < 5 years are overweight

Classification

A) Exogenous obesity: [Most common]

Etiology: **Multifactorial**

- **a. Gene-environment interaction**
- **b. Genetic control of energy expenditure** (specific set point for body weight)
  ↓↓ Energy expenditure → ↑↑ Risk of obesity
- **c. Environmental**
  Type of food: ↑↑calories, ↑↑ CHO, ↑↑ Fat, highly processed
  Physical activity: TV watching, games, computers
- **d. Heredity** (parental obesity specially maternal, familial)
- **e. Leptin deficiency or resistance:** (↑↑ food intake& ↓↓ energy expenditure)

Clinical picture:

- Tall stature (Adult height is normal or low)
- Advanced bone age & early puberty
- Acanthosis nigricans (hyperpigmented hyperkeratotic skin lesion usually in the post. neck or axilla). It is a clinical marker of insulin resistance & ↑↑ risk of type 2 DM

Prevention:

1. Change dietary habits & ↑↑ physical activity
2. Breast feeding ⟶ ↓↓ risk of obesity

Treatment:

1. Dietetic: ↓↓ CHO, ↓↓ fat, ↓↓ calories,↑↑ fibers
2. Life style: ↓↓ TV watching, ↑↑ physical activity
3. Drugs "Not very promising"
   - ↓↓ *Food intake* ⟶ Sympathomimetics, MAO inhibitors
   - ↑↑ *Energy expenditure* ⟶ Ephedrine, caffeine
   - ↓↓ *Fat absorption* ⟶ Orlistat
4. Recombinant leptin: ↓↓ weight, ↑↑ energy expenditure
5. Surgical: gastroplasty

B) Endocrinal:

- **Hypothalamic lesions:** Encephalitis, tumors (craniopharyngioma, optic glioma)
- **Frolich syndrome:** Dwarfism, polyphagia, obesity, DI, hypersomnia
- **Cushing syndrome**
- **Hypothyroidism**
- **Pseudohypoparathyoidism**
- **Stein-Leventhal $:** Obesity, hirsutism, amenorrhea, infertility, polycystic ovaries, inverted FSH / LH ratio (Normally FSH > LH)

C) Congenital syndromes:

- **Laurance-Moon-Biedle $:** Obesity, short stature, mental retardation, polydactyly, syndactyly, retinitis pigmentosa, hypogonadism
- **Beckwith-Wiedemann $:** Fetal overgrowth, macrosomia, macroglossia, polycythemia, visceromegaly (HSM& nephromegaly), omphalocele, hemihypertrophy, hypoglycemia, characteristic ear lobe crease, ↑↑ risk of neoplasms (Wilms tumor)
- **Prader-Willi $:** Hypotonia, hypogonadism, mental retardation, short stature, small hands& feet, early FTT followed by rapid weight gain (1-6 yrs), polyphagia & obesity

  Genetics of Prader-Willi:
  - Deletion of paternally acquired segment of chromosome 15
  - Maternal disomy (Both chromosomes 15 are from the mother)

    (NB: Paternal disomy of chromosome 15 ⟶ Angelman syndrome)

C) Chromosomal:

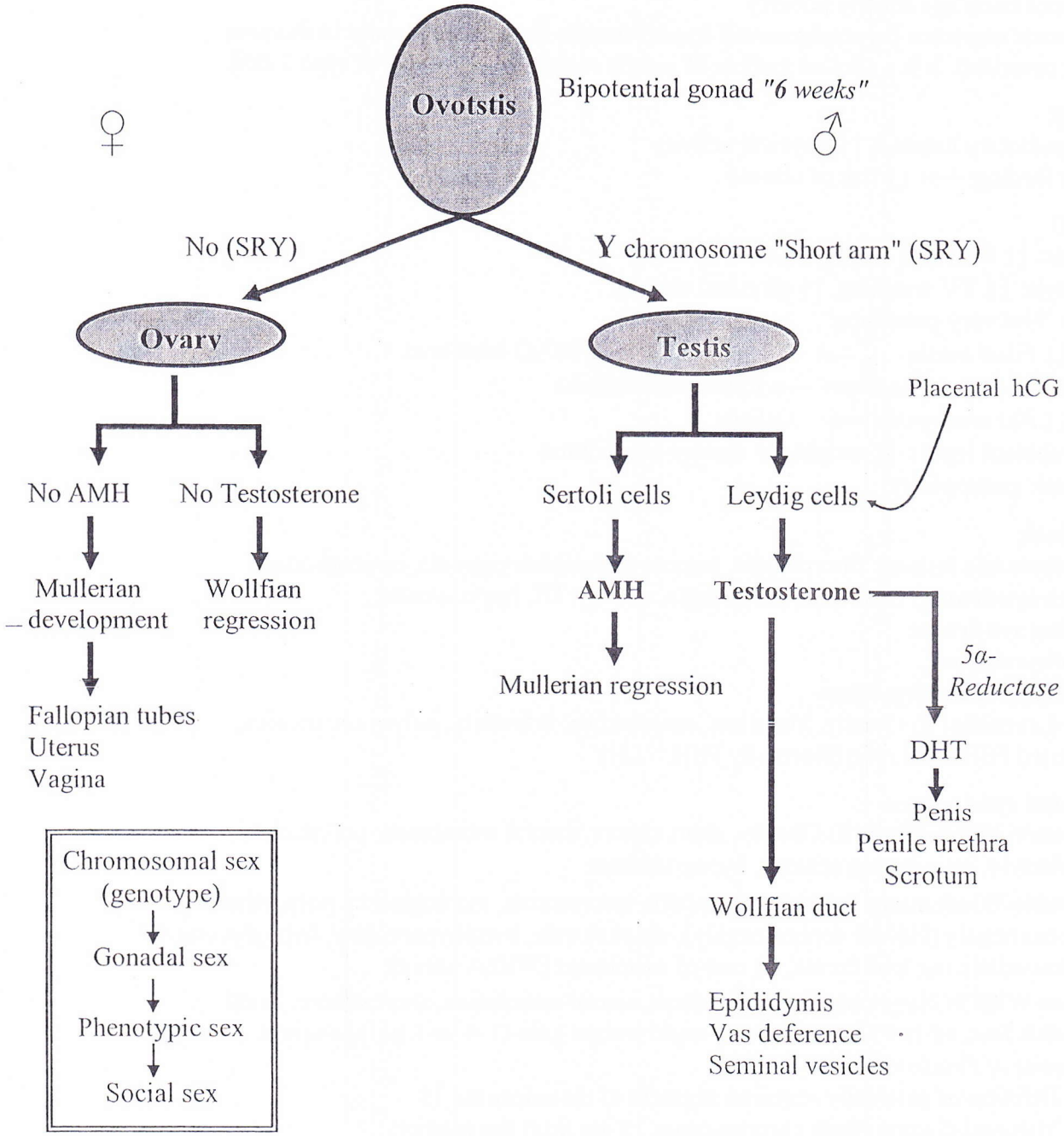
- Turner (XO)
- Down (Trisomy 21)
- Klinefelter syndrome (XXY)
- XXXXY syndrome

Complications of obesity

1. CVS ⟶ HTN, ischemic heart disease, hyperlipidemia& atherosclerosis
2. Respiratory ⟶ Sleep apnea, Pickwickian $, restrictive hypoventilation
3. CNS ⟶ Pseudotumor cerebri, social& behavioral problems
4. GIT ⟶ Fatty liver, cholesterol gall stones, GERD
5. Endocrine ⟶ Insulin resistance, type 2 DM, early puberty, Stein-Leventhal $
6. Joints ⟶ Slipped femoral epiphyses
7. Social & behavioral problems

Approach to a case of obesity:
Dietetic history, Stature, BP, Mentality, Syndromic

Normal Embryonic Sexual Differentiation



Chromosomal sex (genotype)
↓
Gonadal sex
↓
Phenotypic sex
↓
Social sex

- Maleness require Y chromosome short arm (SRY gene) even with multiple X
- X chromosome carrying SRY → XX male syndrome
- SRY deletion / mutation → 46 XY intersex
- No Y chromosome → Ovary (2 X chromosomes are needed; otherwise streak gonads)
- Wollfian development depends on Y chromosome & testosterone
- Female phenotype is the **default pathway**
  - No Y → ovaries
  - No AMH → Mullerian development
  - No testosterone& DHT → Female external genitalia

Intersex & Ambiguous Genitalia

Definition

Intersex (Hermaphroditism): Discrepancy between the morphology of gonads& external genitalia. The new proposed term is disorders of sex development (DSD)
Ambiguous (atypical) genitalia: Sex cannot be identified from external genitalia
Virilized female: Clitoromegaly, labial fusion, labial pigmentation
Incompletely virilized male: Small phallus, small ± undescended testes, bifid scrotum, hypospadias
Microphallus: Penile size < 5th for age; neonate with stretched penile length < 2 cm

Classification

(A) **46, XX Intersex** (Female pseudohermaphroditism): most common form of DSD
(B) **46, XY Intersex** (Male pseudohermaphroditism)
(C) **True hermaphroditism** (True gonadal intersex)

46, XX Intersex (Genotype = XX, Phenotype = virilized ♀)

Causes		Defect	Gonads	Duct	Phenotype	Others
Maternal virilization						
Virilizing maternal tumors (ovarian/adrenal)		Ovarian (androblastoma) Adrenal (adenoma)	Ovaries	M	Virilized ♀ -Clitoral ↑↑ -Labial fusion -Labial pigmentation	Maternal virilization
Androgenic drugs		Progestins	Ovaries	M		
Fetal virilization						
Congenital Adrenal Hyperplasia	21 Hydroxylase	Androgen excess	Ovaries	M	Virilized ♀	No Maternal virilization ↑↑ urinary 17ketsteroids
	11β Hydroxylase		Ovaries	M	Virilized ♀	
	3β (OH) steroid dehydrogenase		Ovaries	M	Mild virilization	
Placental Aromatase deficiency			Ovaries	M	Virilized ♀	
		Fetal adrenal androstenedione & testosterone are converted to estrone& estradiol by placental aromatase				
Other causes						
Idiopathic		Usually associated with GIT or genitourinary defects				

True hermaphroditism (Both testicular & ovarian tissues are present)

Gonads
Testis on one side & ovary on the other
Or bilateral ovotestes

Genotype
46 XX (70% of cases)
46 XX/ 46 XY mosaicism
46 XY

Duct
Both Mullerian& Wollfian duct structures

Phenotype
♂ or ♀ or ambiguous

46, XY Intersex (Genotype=XY, Phenotype = 3 possibilities??)

Causes		Defect	Gonads	Duct	Phenotype	Others
Defects in testicular differentiation		↓↓ Testosterone - No response to hCG Variable C/P according to the *time* of testicular failure				
Deletion of short arm of Y chromosome		No SRY	Streak	M	♀ No puberty	(<8w)
XY pure gonadal dysgenesis (Swyer)		SRY mutation	Streak	M	♀ No puberty	(<8w)
XY gonadal agenesis (8-12 weeks)		Testicular deg. AMH intact	No	No	Ambiguous (≈ near ♀)	(8-12 w) (Testicular regression $)
Bilateral anorchia (>20 weeks)		Testicular deg.	No	W	♂ No puberty	(>20 w) (Vanishing testes $)
Denys-Drash $		Ambiguous genitalia, Glomerulopathy (diffuse mesangial sclerosis), Wilms (usually bilateral). R_X: bilateral nephrectomy + RRT				
WAGR $		Wilms tumor, Aniridia, Genitourinary malformation, Retardation				
Defects in testicular hormones		↓↓ Testosterone - No response to hCG				
Leydig cell aplasia/ hypoplasia		LH receptor defect	Testis	W	♀ or mild virilization	Intact AMH
Testosterone biosynthetic defects	3β (OH) steroid dehydrogenase	Testosterone synthesis defects	Testis	W	♀ or mild virilization No puberty	Salt losing
	20, 22 Desmolase		Testis	W		Salt losing
	17-α Hdroxylase		Testis	W		HTN
	17,20 Desmolase		Testis	W		
	17-Ketosteroid Reductase		Testis	W		
Uterine hernia $ (Persistent Mullerian duct $)		-Absent AMH -AMH receptor defect	Testis (80% Crypto-)	W M	♂ Normal virilization	Acc. discovered during hernia cryptorchidism
Defects in androgen action		Normal or ↑↑ Testosterone - Normal response to hCG – Intact AMH (↑↑ Testosterone: DHT ratio > 17 in 5α Reductase deficiency)				
5-α Reductase deficiency		↓↓Dihydrotesto-strone (DHT)	Testis	W	5 possibilities	Usually reared as ♂
Testicular feminization $ (complete AIS)		End organ resistance	Testis	W	♀ attractive with 2ry sex characters	Amenorrhea Hernia > 50% Orchidectomy?
Partial androgen insensitivity $ (AIS)		Lesser degree of androgen insensitivity	Testis	W	Ambiguous	Early Orchidectomy
Reifenstein $ (Type of partial AIS)		Androgen receptor defect	Testis	W	Incomplete virilization ♂	Reared as ♂
Other causes						
Idiopathic		30% of male intersex				
Smith-Lemli-Opitz $		Microcephaly, ptosis, ambiguous genitalia				

Presentations of XY-intersex

1. Incomplete virilization 2. Ambiguous 3. Complete ♀

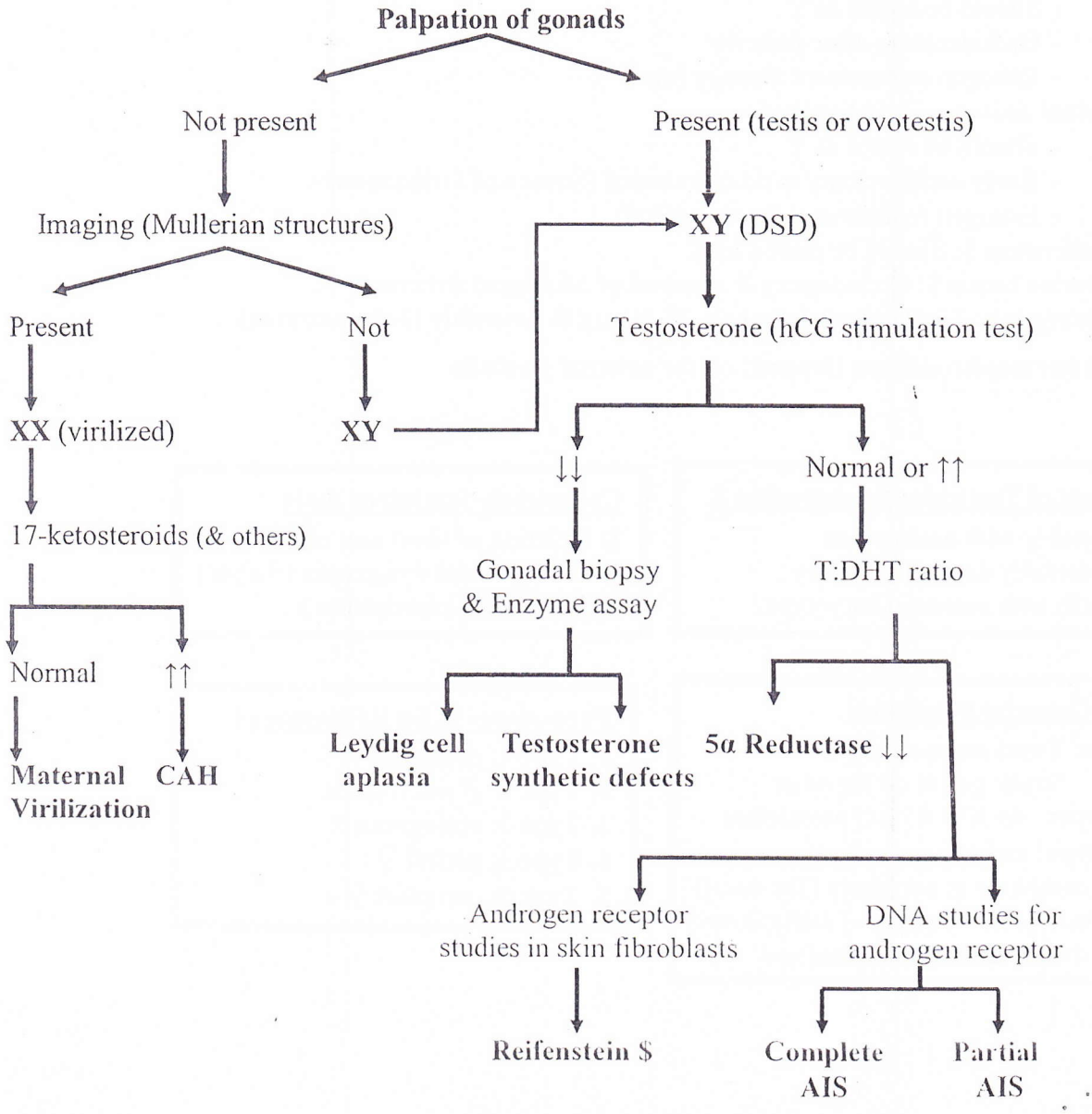
Diagnostic approach to ambiguous genitalia:

Clinical evaluation

- History: Consanguinity, family pedigree, inguinal hernia, infertility, similar conditions, unexplained neonatal deaths, maternal tumors, maternal drugs
- Examination:
  - Maternal virilization (deep voice, hirsutism)
  - Palpation of gonads (testes or ovotestes) in labioscrotal folds& inguinal canal
  - Phallic size, urethral opening, bimanual examination of uterus
  - Manifestations of CAH (FTT, vomiting, dehydration…)

Invetigations

- Karyotyping: to identify genotype (chromosomal sex)
- Serum electrolytes (Na, K), ABG, glucose, 17(OH) progesterone, urinary 17-ketosteroids
- Testosterone, DHT& T:DHT ratio before and after hCG stimulation, FSH, LH
- Pelvic US, CT, MRI for the presence of Mullerian structures (vagina, uterus)
- Genitogram
- Gonadal biopsy
- Open or laparoscopic exploration



Management of ambiguous genitalia:

1. It is medical & psychosocial **emergency** (Sex should be determined within 5 days)
2. Birth **certificate** should not be filled out until sex is identified (avoid neuter names)
3. **Team**: Pediatrician, endocrinologist, geneticist, gynecologist, urologist, psychologist
4. Ambiguous genitalia may be the **clue** for diagnosis of life threatening conditions (CAH)
5. Aim of Rx: To achieve **Cosmetically & functionally** normal external genitalia
6. The sex of **rearing** depends on the appearance of **external** genitalia (phenotype) not chromosomal sex (genotype)
7. Circumcision should be avoided in males with **hypospadias**
8. It is easier to reconstruct external genitalia to create a functional ♀ rather than ♂

(a) Management of adrenal crises in cases of CAH

(b) 46, XX Intersex: should be reared as ♀ **even if highly virilized**. They usually require feminizing genitoplasty (Reduction clitoroplasty, vaginoplasty…)

(c) 46, XY Intersex:

- 5α Reductase deficiency: should be reared as ♂ because masculinization & spermatogenesis normally occur at puberty
- Testicular feminization $:
  - Should be reared as ♀
  - Orchidectomy **after** puberty
  - Estrogen replacement therapy (oral)
- Partial androgen insensitivity $:
  - Should be reared as ♀
  - **Early** orchidectomy is recommended (Source of virilization)
  - Estrogen replacement therapy (Oral)
- Reifenstein $: Should be reared as ♂
- Uterine hernia $: Orchidopexy & removal of Mullerian structures
- Micropenis: Testosterone enanthate 25-50 mg IM monthly (3-dose course)

(d) True hermaphroditism: Depends on the external genitalia

Diagnosis of Testicular feminization $

1. Pupertal ♀ with amenorrhea
2. Accidentally during heriotomy
3. At birth with antenatal karyotype?

Completely feminized male

1. Deletion of short arm of Y
2. Pure gonadal dysgenesis (Swyer)
3. Testicular feminization $

Mixed Gonadal Dysgenesis

Gonads: Testis on one side &
Streak gonad on the other
Genotype: 46 XY/ 45 XO mosaicism
Phenotype: ambiguous*, ♂ or ♀
Rx: - Feminizing genitoplasty (The usual)
- Orchidectomy (Risk of malignancy)
- Estrogen replacement therapy

Phenotypes of 5α Reductase↓↓

1. Type 1: complete ♂
2. Type 2: ♂ micropenis
3. Type 3: ambiguous
4. Type 4: partial ♀
5. Type 5: complete ♀

Hypogonadism

Definition

- Delayed sexual development with no evidence of puberty by the age 13 in ♀& 14 in ♂
- Causes include: Constitutional, hypogonadotropic& hypergonadotropic hypogonadism

Male Hypogonadism	Female Hypogonadism
(A) Primary hypogonadism (= Hypergonadotropic-hypogonadism) Testicular defect ↑↑ Gonadotropins	**(A) Primary hypogonadism** (= Hypergonadotropic-hypogonadism) Ovarian defect ↑↑ Gonadotropins
(B) Secondary hypogonadism (= Hypogonadotropic-hypogonadism) Hypothalamic/pituitary defect ↓↓ Gonadotropins (FSH & LH)	**(B) Secondary hypogonadism** (= Hypogonadotropic-hypogonadism) Hypothalamic/pituitary defect ↓↓ Gonadotropins (FSH & LH)

Male Hypergonadotropic-Hypogonadism

Etiology

1. **Congenital anorchia:** Testicular damage after sexual differentiation
2. **Defects of androgen production:** see before (46 XY-DSD)
3. **Rudimentary testes:** (AR or XLR) "Very small testes"
4. **Germ cell aplasia (Del Castillo $ or Sertoli cell only$):**
   - Leydig cells: normal ⟶ normal testosterone ⟶ normal sexual differentiation
   - Seminiferous tubules (absent Sertoli cells) ⟶ Small testes, azoospermia, infertility
   - No inhibin (normally secreted by Sertoli cell) ⟶ ↑↑ FSH with normal LH
5. **Klinefelter (47, XXY male):** (1/1000)
6. **45, X male:** Yp segment is translocated to another chromosome
7. **XX male:** Paternal X-Y Crossing over involving SRY gene
8. **XXX male:** Paternal X-Y Crossing over AND maternal X-X non-disjunction
9. **Noonan Syndrome:** (1/1000)
10. **Testicular damage**
    - Bilateral torsion (Vascular)
    - Surgical trauma during correction of cryptorchidism
    - Radiotherapy & chemotherapy
    - Acute orchitis: Mumps in pubertal ♂

Noonan Syndrome:

- Etiology: AD (variable expression)
- Features of Turner $ + Normal karyotyping + affecting ♀& ♂
- Short stature, neck webbing, cubitus valgus
- CHD: PS
- Facies: Hypertelorism, epicanthus, ptosis, micrognathia, antimongloid slant, ear anomalies
- Hypogonadism: Delayed puberty (2 yrs later)
  ♂: Small testes, cryptorchidism
  ♀: Premature ovarian failure
- Mental retardation: 25%
- Rx: hGH

Klinefelter Syndrome:

Genetic types:

- Non-disjunction (most common)
- Mosaicism (better prognosis)
- Variants: XXXY, XXXXY (↑↑ Severity)

C/P: as in ♂ 1ry hypogonadism + some MR + learning disability + behavioral disorders

Investigations:

Complications:

Breast cancer, mediastinal germ cell tumors

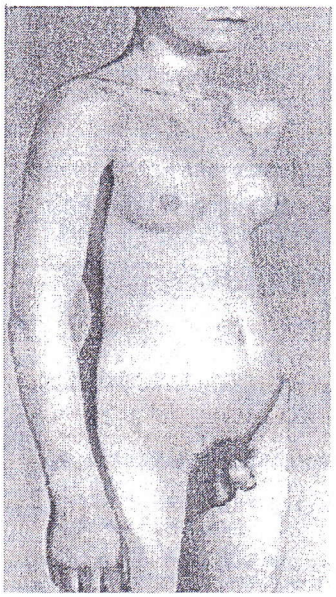
Rx:

Poly-Y male (47, XYY male):

No Hypogonadism

Aggressive antisocial behavior& violence

Clinical picture



1. **Onset:** Usually present as delayed puberty
   May be suspected at birth (Micropenis & small testes)
2. **Measurements:** Tall stature; span > height, LS > US ***(Eunuchism)***
3. **Testes:** Absent or small (Prader Orchidometer)
4. **Secondary sex characters fail to develop:**
   - **Hair (facial, axillary, pubic):** scanty
   - **Acne:** absent
   - **Voice:** high pitched
   - **Fat distribution:** feminine (buttocks, breast)
   - **Penis& scrotum:** infantile
5. **Gynecomastia**
6. **Infertility** (Azoospermia)
7. **Picture of the cause**

Investigations

1. Testosterone level: ↓↓
2. Gonadotropins "FSH & LH": ↑↑ (specially > 11 yrs)
3. hCG stimulation test: No response [Normally hCG ⟶ ↑↑ Testosterone at ***any*** age]
4. AMH & Inhibin level
5. Karyotyping (XXY…)
6. Azoospermia
7. Testicular biopsy (In Klinefelter $: Hyalinized seminiferous tubules)

Side Effects of sex steroids
- Lipid abnormalities
- Thromboembolism
- Acne
- HTN

Treatment

- Long-acting **testosterone enanthate**, starting at 11-12 yrs (Why?)
  Dose: 50 mg IM / 3-4 wks, ↑↑ by 50 mg every 6-9 months till 200 mg / 3-4 wks
- **Intracytoplasmic sperm injection (ICSI):** ?? fertility

Male Hypogonadotropic-Hypogonadism

Etiology

1. **Hypopituitarism:** Transcription factors & TTIIIIE
2. **Isolated deficiency of gonadotropins:**
   - Sporadic
   - Familial
3. **Genetic defects:**
   - Kallmann $ (XLR, AR, AD) " hypogonadism, **anosmia**, mid-facial & renal defects"
   - DAX-1 gene mutation causing adrenal hypoplasia & impaired GnRH secretion
4. **Congenital syndromes**
   - Laurance-Moon Biedl
   - Prader-Willi

Clinical picture

- As C/P of primary hypogonadism
- Picture of the cause (Microphallus in hypopituitarism, anosmia in Kallmann $)

Investigations

1. Testosterone level: ↓↓
2. Gonadotropins "FSH& LH": ↓↓ with absence of nocturnal pulsatile LH secretion
3. hCG stimulation test: ↑↑ Testosterone
4. GnRH stimulation test: Blunt GTH response (DD: Constitutional delayed puberty)
5. Other pituitary hormones (GH, ACTH) & imaging
6. DNA probes for different mutations (Kallmann $)

Differential Diagnosis

Constitutional delayed puberty: "Not uncommon = 3 %"

Diagnosis: If no puberty (Testicular volume < 4 mL) by the age of 14-15 yrs & testosterone level < 50 ng/dL. It should be differentiated from hypogonadotropic-hypogonadism;

- **Family history:** +Ve
- **Single 8 A.M. Testosterone level:** is a good predictor of impending puberty
- **Nocturnal pulsatile LH secretion:** may be detected
- **GnRH stimulation test:** ↑↑ LH
- **Treatment:** Testosterone enanthate, 100 mg IM/4 wks, for 4-6 months

  Value:
  - Increase 2ry sex characters (relieves anxiety)
  - May initiate puberty (↑↑ Growth & ↑↑ Bone age)
  - DD: from Hypogonadotropic-hypogonadism (Diagnostic therapeutic test)

Treatment

- Constitutional delayed puberty should be **ruled out**
- Established cases (pubertal changes regress after discontinuation of testosterone):

a. **Testosterone enanthate**, starting at 11-12 yrs
Dose: 50 mg IM/3-4 wks, ↑↑ by 50 mg every 6-9 months till 200 mg/3-4 wks ⟶ Development of 2ry sex characters but with *small sized testes*

b. **hCG (*Pregnyl*):** IM 500-1000 IU, 3 times weekly ⟶ stimulates testicular growth & spermatogenesis. If testicular ↑↑ is not sufficient after 6-12 months, add:

c. **Human menopausal gonadotropin (HMG)"*Humegon*"**: IM 37.5-150 IU, 3 times/ wk

d. **Episodic administration of GnRH:** programmable infusion pump (Very expensive)

Prognosis

Spermatogenesis can be achieved after proper Rx (up to 2 yrs)

Female Hypergonadotropic-Hypogonadism

Etiology

1. **Turner syndrome (45, XO):** (1/2000)
2. **Noonan $:** Differences??
3. **XX Gonadal dysgenesis (Pure gonadal dysgenesis):** Gonads as Turner, No somatic features
4. **Mixed gonadal dysgenesis:** see before
5. **XXX female:** Non disjunction, No hypogonadism, learning& behavioral disorders
6. **XXXX & XXXXX female:** Hypogonadism + MR
7. **Resistant ovary syndrome:** FSH receptor defect
8. **Ovarian damage**
   - Radiotherapy& chemotherapy
   - Galactosemia
   - Denys-Drash syndrome
   - Ataxia telangiectasia
   - Immune ovarian failure

	Turner	Noonan
Sex	Only ♀	♀& ♂
Genetics	Non-disjunction	AD
Cardiac	CoA / bicuspid aotic valve	PS
Mentality	MR in 18%	MR more common
Sexual Development	Hypogonadism	Delayed (2yrs)

Turner Syndrome

Genetic Types

- ☒ Non-disjunction (most common): The X chromosome is usually of maternal origin
- ☒ Mosaicism (better prognosis): 45, X / 46, XX

Clinical picture

(A) At birth: Edema of dorsum of hands & feet

(B) Childhood:

- Short stature (mean = 143 cm)
- Webbing of the neck
- Widely spaced nipples
- Cubitus valgus (↑↑ carrying angle)
- Low posterior hair line
- Normal mentality (MR in 18%)
- Cardiac: Coarctation, bicuspid aortic valve
- Renal: Hoarseshoe, ectopic kidney…
- Thyroiditis (30%)
- IGT, Type II DM

(C) Puberty:

- Secondary sex characters fail to develop

Investigations

1. Estrogen level: ↓↓
2. Gonadotropins "FSH& LH": ↑↑ (specially > 11 yrs)
3. Karyotyping (45, X)
4. U/S, Echocardiography, Thyroid profile

Treatment

- **hGH**
- **Estrogens:** To induce the development of 2ry sex characters. Start at 11-12 yrs (Why?)
- **Estrogen + Progesterone cyclic therapy:**
  - Estrogen D1- D23
  - Progestrone D10- D23
  - No Rx D23-D30 ⟶ Withdrawal bleeding
- **Ovum donation + IVF:** ?? Fertility

Female Hypogonadotropic-Hypogonadism

Etiology

1. **Hypopituitarism:** Transcription factors& TTIIIIE
2. **Isolated deficiency of gonadotropins:**
   - Sporadic
   - Familial
3. **Genetic defects:**
   - Kallmann $ (XLR, AR, AD) " hypogonadism, anosmia, mid-facial& renal defects"
4. **Congenital syndromes**
   - Laurance-Moon Biedl
   - Prader-Willi
5. **Anorexia nervosa**

Clinical picture

- As C/P of primary hypogonadism
- Picture of the cause (anosmia in Kallmann syndrome)

Investigations (as in 2ry ♂ hypogonadism)

Treatment Constitutional delayed puberty should be **ruled out**

Gynecomastia

Definition

Enlargement of the male breast due to hypertrophy of the glandular tissue

Etiology

1. **Physiological**
   a. **Neonatal:** Transplacental passage of maternal estrogens
   b. **Pubertal** (65% of all ♂): ↑↑ aromatase activity. Bilateral or unilateral & tender
2. **Pathological**
   a. **Endocrinal:** Male hypoganadism (Klinefelter syndrome)
   b. **Liver cell failure** (↓↓ estrogen metabolism)
   c. **Neoplastic:** Feminizing tumors (testicular & adrenal)
      Prolactinoma
      Bronchogenic carcinoma (Paramalignant syndrome)
   d. **Drugs:** Estrogens, spironolactone, digitalis, cimetidine, ketoconazole
   e. **Idiopathic**

Cryptorchidism

DD of empty scrotum:
1. Absent testes
2. Retractile testes
3. Undescended testes

Definition

Failure of descent of one or two testes

Incidence

Term = 3.4% Preterm = 30% Spontaneous descent occurs in the majority

If No descent by the age of 4 months, the testis will remain undescended

Factors affecting testicular descent

1. **Hormonal**
   Testosterone, DHT & AMH
2. **Mechanical**
   Gubernaculum, epididymis & abdominal pressure

Retractile testis:
Brisk cremastric reflex
Testes can be brought down to the scrotum

Classification

1. Abdominal
2. Inguinal
3. Gliding
4. Ectopic (Superficial inguinal, perineal)

Investigation

1. Testosterone before & after hCG stimulation: to detect functioning testicular tissue & exclude anorchia
2. U/S, CT, MRI abdomen
3. Laparoscopy

Complications

1. Infertility (Testicular pathological changes start to occur by 6-12 months)
2. Malignancy (1/40-80)
3. Psychological

Treatment (*Before 9-15 months, ideally at 6 months)*

1. **Hormonal**
   a. **hCG (Pregnyl):** IM 3000 IU/ wk for 4 weeks; or
   b. **GnRH**
2. **Surgical** (*Orchidopexy)*

Thyroid Gland

Physiology of thyroid hormones

-Thyroid hormones:

- Tetraiodothyronine or Thyroxine (T_4)
- Triiodothyronine (T_3)

MIT= Monoiodotyrosine
DIT= Diiodotyrosine

-Formation of thyroid hormones:

- **Iodide trapping:** against both electrical& concentration gradients
- **Oxidation:** oxidation of iodide to iodine ***"Peroxidase"***
- **Organification of iodine (= Iodination of tyrosine):** ⟶MIT& DIT (inactive)
- **Coupling:** DIT + DIT ⟶ T_4 DIT + MIT ⟶ T_3 ***"Peroxidase"***
- **Storage:** bound to thyroglobulin in the colloid
- **Release:** by endocytosis & proteolysis of thyroglobulin⟶ release of T_4*& T_3
  NB: Free MIT & DIT are normally deiodinated; iodine is reused "***Deiodinase"***

-Transport of thyroid hormones:

- The majority of T_3& T_4 is bound to plasma proteins *(reserve or storage form)*
  - Thyroxine-binding globulin (TBG)
  - Albumin
  - Prealbumin
- The free part is the physiologically active
- T_4 is more abundant (50 times T_3 concentration)
- 80% of circulating T_3 is formed by deiodination of T_4
- T_3 less bound shorter half-life more rapid action more active (3-5 times)
- T_4 is converted to T_3 in peripheral tissues (cytoplasm)⟶nuclear receptors

-Control of secretion:

- **TRH:** ↑↑ TSH, ↑↑ prolactin
- **TSH:** ↑↑cAMP⟶↑↑ size, ↑↑ vascularity, ↑↑ function
- **Feedback:** by the *free* part of thyroid hormones
- **Iodine:** ↓↓ Iodine⟶↓↓ T_4& T_3⟶↑↑ TSH ⟶ Goiter
  ↑↑ Iodine ⟶ attenuate the TSH action on thyroid "Wolff-Chaikoff effect"

Trapping
Organification
Coupling
Release

-Action &side effects:

- Calorigenic⟶↑↑ O_2 consumption, ↑↑ Metabolic rate (BMR), ↑↑ Heat production
- CHO ⟶ ↑↑ GIT absorption; ↑↑ glycolysis, ↑↑ glycogenolysis, ↑↑ gluconeogenesis
- Fats ⟶ ↓↓ cholesterol level (↑↑ LDL receptors)
- Ptn ⟶ Anabolic in physiologic dose, catabolic in large dose
  Myopathy (Myopathy& weakness occur in hyper-& hypothyroidism)
  Osteoporosis
- Bone ⟶ ↑↑ Bone age (in hypothyroidism ⟶ Delayed growth& bone age)
- Vitamins ⟶ Conversion of carotene to vitamin A
  ↑↑ Vitamin B_{12} absorption
- Blood⟶↑↑ Erythropoiesis
- CVS ⟶ ↑↑ No & affinity of β-receptors in the heart (↑↑ catecholamine effect)
  ↑↑ HR, ↑↑ stroke volume, ↑↑ systolic BP, peripheral VD, ↑↑ pulse pressure
- CNS ⟶ Important for the rapidly growing brain (synapses, myelination)
- Growth ⟶ Necessary for GH& IGF-1 synthesis & action
- Sexual maturation ⟶ Delayed in hypothyroidism (precocious puberty may...)

Iodine metabolism:
Daily requirement: 30-150 µg/day **Sources:** near sea, iodized table salt

Investigations of Thyroid Disease

I For assessment of thyroid functions

1. Serum total T_4 & T_3

- Normal values: T_4 = 4-11 µg/dL
  T_3 = 60-200 ng/dL
- Affected by changes in TBG
- TBG is ↑↑ in: - Congenital - Neonates
  - Estrogens (OCPs) - Pregnancy
- TBG is ↓↓ in: - Congenital - Liver failure
  - Androgens - Congenital nephrosis

2. Free T_4 & T_3

The most accurate, not affected by TBG

3. Resin T_3 uptake

Known amount of radioactive T_3 is added to the patient's serum to bind free TBG. The remaining unabsorbed T_3 is absorbed by resin. It is a measurement of free TBG. Resin T_3 uptake is ↑↑ in hyperthyroidism (↓↓ free TBG)

4. Serum TSH (Normal values = 6 µU/ mL)

- TSH is ↑↑ in: - Primary hypothyroidism
  - TSH-secreting pituitary tumor
- TSH is ↓↓ in: - Hyperthyroidism
  - Secondary hypothyroidism (central)

5. TRH stimulation test (used in secondary hypothyroidism)

- ↑↑ TSH & prolactin suggests hypothalamic lesion (not pituitary)
- No response occurs in pituitary lesions& TRH unresponsiveness (No ↑↑ TSH)

6. Radioactive iodine uptake (^{99m}Tc, I^{123}, I^{132})

↑↑ Uptake ⟶ Hyperthyroidism
↓↓ Uptake ⟶ Hypothyroidism

II For detection of the cause

1. Thyroid scanning (^{99m}Tc, I^{123}, I^{132})

Indications

- Detection of ectopic thyroid gland e.g. lingual thyroid
- Detection of retrosternal goiter
- Solitary thyroid nodule; hot, cold or warm

2. Serum thyroglobulin

↑↑ in hyperthyroidism & differentiated thyroid carcinoma (tumor marker)

3. Thyroid US, CT& MRI

To detect size& location of the gland and the nature of solitary nodule (cystic/solid)

4. Fine needle aspiration cytology (FNAC) & biopsy

5. Thyroid autoantibodies

6. Detection of the cause of defective hormone synthesis

- **Iodide trapping:** Radioactive iodine uptake
- **Organification:** K-perchlorate competes with radioactive iodine for uptake &storage. In organification defects ⟶ ↑↑ discharged iodine from the thyroid
- **Coupling:** ↑↑ MIT& DIT in thyroid biopsy
- **Storage:** absent thyroglobulin ⟶ ↓↓ T_4 ⟶ ↑↑ TSH ⟶ Goiter
- **Release** *"Deiodinase defect"*: ↑↑ MIT& DIT in blood& urine

III Non-specific tests

1. **CBC:** Anemia in hypothyroidism
2. **Cholesterol:** ↑↑ in hypothyroidism
3. **Carotene:** ↑↑ in hypothyroidism
4. **Calcium:** ↑↑ in hyperthyroidism
5. **Glucose:** ↓↓ in hypothyroidism
6. **GH:** ↓↓ in hypothyroidism
7. **Basal metabolic rate (BMR):** ↑↑ in hyperthyroidism, ↓↓ in hypothyroidism
8. **X-rays:**
   - Bone X-ray: Delayed bone age
     Absent distal femoral ossific center
   - Chest X-ray: Pericardial effusion
9. **ECG:** Bradycardia, low voltage (Hypo-)
10. **EEG:** Low voltage

IV Neonatal screening

Screening programs: from the 3rd to 7th days

	North America	Europe& Japan
Technique (Heel prick)	Measurement of T_4 (↓↓ < 5 µg/dL)	Measurement of TSH (↑↑ > 20 µU/mL)
Advantages	Identify: ▪ 1 ry hypothyroidism ▪ 2 ry hypothyroidism ▪ ↓↓ TBG ▪ Patient with delayed ↑↑ in TSH	Identify: ▪ 1 ry hypothyroidism ▪ Subclinical hypothyroidism (normal T_4, ↑↑ TSH)
Disadvantage Missed cases	Subclinical hypothyroidism (normal T_4, ↑↑ TSH)	▪ Patients with ↓↓ TBG ▪ Delayed ↑↑ in TSH ▪ Secondary hypothyroidism

Regardless of the approach used in screening, some infants escape detection; clinicians should maintain their awareness of the early manifestations of hypothyroidism

No thyroid tissue by scanning:
- Aplasia
- Transplacental TRBAb
- Trapping defect

Pendred syndrome:
Defect in organification due to defect in SO_4 transport protein
- Goiter
- Deaf-mutism
- Thyroid status: eu- or hypo-

Investigations: +ve perchlorate test
Rx: Thyroid hormone + Hearing aids

Congenital Hypothyroidism (Cretinism)

Definition

Deficient production of thyroid hormone or defect in receptor activity (since birth)

Etiology (Goiter = *)

(A) Primary hypothyroidism:

1. Thyroid dysgenesis (most common cause = 85% of all cases)

- Aplasia (thyroid scanning fail to detect any thyroid tissue)
- Hypoplasia
- Ectopic (Lingual, sublingual, subhyoid) variable onset of manifestations

2. Defective hormone synthesis* (dyshormonogenesis = 10% of cases)

- Iodide trapping
- Organification
- Coupling
- Pendred syndrome
- Deiodination defect
- Storage (# Thyroglobulin synthesis)

3. Thyroid hormone unresponsiveness* (End organ resistance = receptor defect) AD

- ↑↑ T_3& T_4 ⟶ but clinically "Euthyroid"
- Normal or ↑↑ TSH i.e., No TSH suppresion

DD: - TSH secreting pituitary tumor
- Graves disease ↓↓ TSH

4. Iodine deficiency*(maternal)

- Mild-moderate ⟶ ↓↓ T_4 ⟶ ↑↑ TSH ⟶ Goiter "Euthyroid"
- Severe (endemic goiter) ⟶ Goiter but decompensation "Hypothyroidism"

5. Iodine exposure*

- Iodine containing antiseptics used in CS, NICU or surgical procedures "transient"
- Amiodaron therapy (high iodine content)

6. Maternal medications

- Radioactive Iodine (I^{131})
- Amiodarone, methimazole, propylthiouracil*

7. Maternal antibodies "transient"

Transplacental passage of thyrotropin receptor blocking antibodies (TRBAb) ⟶ inhibits TSH binding to receptors (thyroid scanning fails to detect any thyroid tissue but US may show). TRBAbs may be present in mothers with auto immune thyroid disease (Graves, Hashimoto...)

(B) Secondary:

1. **TSH or TRH deficiency:** Isolated or multiple, pituitary or hypothalamic (T T I I I I E)
2. **TSH unresponsiveness:** (↓↓ T_4, ↑↑ TSH, No response to exogenous TSH)
   It may occur as a part of type Ia PHP
3. **TRH unresponsiveness:** TRH receptor defect. No response to TRH (No ↑↑ TSH)

Clinical picture ♀:♂ = 2:1

A) **At Birth:** Asymptomatic at birth (maternal T_4).Diagnosis is now largely dependent on screening. Clinical manifestations usually appear in 1st few weeks

B) **Early manifestations of congenital hypothyroidism**

Prolonged gestational age
Prolonged physiologic jaundice > 2-3 weeks
Prolonged sleep
Poor feeding
Weak hoarse cry
Abdominal distension
Delayed passage of meconium & constipation
Open posterior fontanel
Hypothermia & mottling

C) **Late Manifestations** (*The full-blown picture develop within 3-6 months*)

a. **Delayed mental development:** Social smile, recognition of mother…

b. **Delayed motor development:** Head support, sitting…

c. **Delayed sexual development** (but precocious puberty may occur...)

d. **Physical features:** (*The full-blown picture develop within 3-6 months*)

☒ **Vital signs**

- **HR:** Bradycardia
- **Temperature:** Hypothermia

☒ **Anthropometric measurements:** Short stature (Infantile proportion)

- US/LS: 1.7:1
- Height > span
- Short limbs

☒ **Systemic examination**

- Head: Delayed closure of anterior fontanel, open posterior fontanel
- Hair: Coarse, scanty, brittle and low anterior hair line
- Forehead: Short, wrinkled
- Eye: Puffiness of eyelids (Myxematous tissue)
- Nose: Depressed nasal bridge
- Tongue: Large, protruding (DD: Down syndrome)
- Lips: Pallor
- Teeth: Delayed dentition
- Neck: Short & thick ± Goiter, When?
- Fat deposition above the clavicles
- Abdomen: Abdominal distension, umbilical hernia
- Skin: Dry, scaly?, cold?, pale?, yellowish (↑↑ Carotene), myxedema (Non-pitting)
- Hands: Short & broad with short fingers & dorsal pad of fat
- Myopathy: Waddling gait
- CVS: Bradycardia, cardiomegaly, asymptomatic pericardial effusion

Investigations

Treatment "*Replacement therapy*"

Sodium-L-thyroxine *(Eltroxin 50, 100 μg tablets)*

Dose: Neonates 10-15 μg/kg/day, then 4-8 μg/kg/day. Usual daily dose 100-300 μg/d

Duration: Lifelong. To exclude transient causes, stop Rx at the age of 3 yrs for 3 wks
⟶ Marked ↑↑ TSH in children with permanent hypothyroidism

Monitoring of Rx:

1. Clinical — Clinical improvement (maximum response occurs after 6 weeks)
   Overdose ⟶ diarrhea, fever, tachycardia, sweating
   Assessment of height / 3 months
   Assessment of bone age / 6 months
   Assessment of IQ
2. Laboratory (T_4, TSH)

Side effects:

- Overdose
- Craniosynostosis
- Pseudotumor cerebri

Prognosis

Early diagnosis & treatment (Before the 3rd month of age) ⟶ Better prognosis

Acquired Hypothyroidism (Juvenile)

Definition

Symptoms of hypothyroidism appear after a period of apparently normal thyroid function (DD: Congenital hypothyroidism with late presentation)

Etiology

1. Autoimmune
- Lymphocytic thyroiditis "Hashimoto's thyroiditis" (Most common cause)
- Type II autoimmune polyendocrinopathy (Thyroid, IDDM)

2. Iatrogenic
- Methimazole, propylthiouracil
- Thyroidectomy
- Radioactive Iodine (I^{131})
- Irradiation (for malignancy & before bone marrow transplantation)
- Amiodarone
- Iodine exposure (potassium iodide, cough mixtures for asthma)

3. Systemic diseases
- Nephropathic cystinosis
- Congenital nephrosis
- Histiocytosis

4. Severe Iodine deficiency

5. Thyroid hormone unresponsiveness (End organ resistance): usually "Euthyroid"

Clinical picture

A) **Physical:** Decelerated growth, delayed bone age, cold intolerance, constipation ± Goiter
B) **Mental:** Sleepiness
C) **Sexual:** Delayed puberty (precocious puberty may occur...)

Investigations & Treatment *"of the cause + Replacement therapy"*

Thyroiditis

Etiology

1. **Lymphocytic thyroiditis "Hashimoto's thyroiditis"** (most common cause)
2. **Acute suppurative thyroiditis**
   - Organism: Anaerobic ± aerobic
   - Most common organisms: Strept.viridans & Staph.aureus
   - Local manifestations: Swelling, redness, hotness, tenderness ± abscess formation
   - Systemic manifestations: often absent
   - Laboratory: leucocytosis, ↓↓ radioactive iodine uptake
   - Thyroid function: usually normal (hyperthyroidism may occur due to escape of thyroid hormones)
   - Treatment: Antibiotics ± abscess drainage
3. **Subacute non-suppurative thyroiditis (De Quervain disease)**
   - Etiology: viral infection (mumps…) usually on top of lymphocytic thyroiditis
   - Local manifestations: vague pain& tenderness
   - Systemic manifestations: low grade fever
   - Thyroid function: usually hyperthyroidism (due to escape of thyroid hormones)
   - Laboratory: ↑↑ ESR, ↓↓ radioactive iodine uptake
   - Treatment: spontaneous remission (months) → Euthyroid → Hypothyroid state
4. **Chronic thyroiditis** (TB, sarcoidosis)

Lymphocytic thyroiditis

(Hashimoto's thyroiditis)

Definition

It is the commonest cause of acquired hypothyroidism

Etiology

Autoimmune

Pathogenesis (= Evidence of immune nature)

1. **Lymphocytic infiltration of the thyroid** (T& B cells)
2. **Thyroid autoantibodies**
   - Antiperoxidase antibodies
   - Antithyroglobulin antibodies (ATA)
   - Thyrotropin receptor blocking antibodies (TRBAb)
   - Thyroid stimulating immunoglobulins (TSI)
   - Thyroid growth stimulating immunoglobulins (TGSI)
3. **Associated disorders**
   - Type I autoimmune polyendocrinopathy (HAM syndrome)
   - Type II autoimmune polyendocrinopathy (Thyroid, IDDM, Addison's disease)
   - Pernicious anemia, vitiligo, alopecia, celiac disease
   - Type I DM
   - Myasthenia gravis
   - Down, Turner, Klinefelter syndromes

Clinical picture

Age: Any age usually > 6 yrs **Sex:** ♀: ♂= 5:1

A) **Goiter:** Diffuse, firm, non-tender (stationary / spontaneous regression)

B) **Thyroid state:**
   - **Euthyroid:** most common at the onset
   - **Hypothyroid:** many patients develop hypothyroidism within years
   - **Hyperthyroid:** (Hashitoxicosis)

C) **Associated disorders:**

Investigations

- Thyroid functions (↓↓ T_4& T_3, ↑↑ TSH, +ve Perchlorate test, US)
- Thyroid autoantibodies
- Biopsy: rarely indicated

Treatment

- Periodic evaluation
- Sodium-L-thyroxine *(Eltroxin 50, 100 μg tablets)* in hypothyroidism

Hyperthyroidism

Definition

Excessive secretion of thyroid hormones

Etiology

1. **Graves disease** (Diffuse toxic goiter)
2. **Toxic nodular goiter** (Plummer disease)
3. **Lymphocytic thyroiditis "Hashitoxicosis"**
4. **Acute & subacute non-suppurative thyroiditis (De Quervain disease)**
5. **TSH secreting pituitary tumor**
6. **Activation mutation of TSH receptor**
7. **McCune Albright syndrome**
8. **Hyperfunctioning thyroid adenoma or carcinoma**
9. **Transient neonatal thyrotoxicosis** (Infants born to mothers with Graves disease)
10. **Thyrotoxicosis factitia** (↑↑ T_4, ↓↓ TSH & very low thyroglobulin level)

Graves Disease

Definition

It is the commonest cause of hyperthyroidism

Etiology

Autoimmune

Pathogenesis (= Evidence of immune nature)

1. **Lymphocytic infiltration of the thyroid** (T & B cells)
2. **Thyroid autoantibodies**
   - Thyrotropin receptor stimulating antibodies (TRSAb) ⟶ ↑↑ TSH receptors
   - Thyrotropin receptor blocking antibodies (TRBAb)
   - Exophthalmogenic immunoglobulin (EI) ⟶ ↑↑ GAG in retro-orbital tissue
3. **Associated disorders** (see before)

Clinical picture

Age: usually 11-15 yrs **Sex:** ♀: ♂= 5:1

A) **Local manifestations (Goiter):**
Diffuse, soft, smooth surface, non-tender ± bruit (upper poles)

B) **Systemic manifestations:**
- Insomnia, irritability, nervousness, tremors, ↑↑ reflexes
- Heat intolerance, ↑↑ sweating, warm moist hands
- Loss of weight in spite of good appetite
- Palpitation, tachycardia, arrhythmia, big pulse volume
- Weakness (Myopathy), easy fatigability
- ↑↑ Stool frequency (Diarrhea)
- Polyuria
- Menstrual irregularities, loss of libido
- RES hyperplasia (Spleen & LN)
- Patchy dermopathy (pigmentation…)

C) Ophthalmopathy:

- **Pain, photophobia, blurring of vision, bulging**
- Exposure keratitis
- Periorbital edema
- Exophthalmos
- *Stellwag's sign:* staring look with infrequent blinking
- *Mobius' sign:* defective convergence (muscle weakness)
- *Von Grafes' sign:* lid lag when looking downwards
- *Dalrymple's sign:* appearance of a rim of sclera above the cornea

DD of Graves disease:
1. Hyperthyoidism
2. Thyroid hormone unresponsiveness

D) Thyrotoxic crisis (follows thyroid surgical manipulation, trauma or infection)
Hyperpyrexia, excessive sweating, tachycardia, arrhythmia, coma, convulsions

Investigations

- Thyroid functions (↑↑ T_4& T_3, ↓↓ TSH, ↑↑ Thyroglobulin)
- Thyroid autoantibodies…
- Radioactive iodine uptake ↑↑

Treatment

A) Medical treatment:

1. **Sedatives:**
2. **β-adrenergic blockers:** Propranolol ⟶ # Catecholamine action (Cardioprotector)
   Dose: 0.5-2 mg / day divided every 8 hrs
3. **Anti-thyroid drugs (Methimazole, Propylthiouracil)**
   - Action: # Organification
     ↓↓ TRSAb
     PTU ⟶ inhibits peripheral conversion of T_4 to T_3
   - PTU has lesser ability to cross the placenta& to pass in breast milk
   - Dose: Methimazole = 0.5-1 mg / day single daily dose
     PTU = 5-10 mg/ day divided every 8 hrs
   - Side effects:
     - Allergy (rash) & Agranulocytosis (monitor with CBC)
     - ↑↑ TSH, ↑↑ size& vascularity of thyroid
     - ↑↑ Exophthalmos
     - Liver, kidney, GIT

B) Subtotal thyroidectomy:

- Indication: Failure of medical treatment
- Preoperative preparation: Methimazole or PTU ⟶ Euthyroid state (2-3 months)
  Lugol's iodine ⟶ ↓↓ Size & vascularity (in the last 2 wks)
- Complications:
  - Hypothyroidism
  - Hypoparathyroidism
  - Vocal cord paralysis (recurrent laryngeal nerve injury)
  - Thyrotoxic crisis

C) Radioactive iodine (I^{131}): in children >10 yrs
Complications: Hypothyroidism, adenoma formation

D) Treatment of ophthalmopathy: Prednisone or radiotherapy

E) Treatment of Thyrotoxic crisis: Propranolol, Temperature control, PTU, Iodide, Hydrocortisone, IVF, Rx of precipitating factor (infection)

Goiter

Definition

It is thyroid enlargement (whatever the etiology). It may be associated with euthyroidism, hypothyroidism or hyperthyroidism. It may be congenital or acquired

Etiology

1. **Simple** (Non-toxic, non-neoplastic, non-inflammatory thyroid enlargement)
   - Physiological: usually occurs in pubertal ♀due to relative iodine deficiency ⟶*(Venus neck).* **Rx:** Reassurance, L-thyroxine may be indicated
   - Simple nodular goiter: repeated cycles of stress& fluctuation of TSH levels
   - Colloid goiter: intermediate stage
2. **Toxic goiter**
   - Graves (Diffuse toxic goiter)
   - Plummer disease (Nodular toxic goiter)
   - Toxic nodule (autonomous function with suppression of the rest of the gland – hot nodule on scanning)
3. **Inflammatory**
   - Lymphocytic thyroiditis
   - Acute suppurative thyroiditis
   - Subacute non suppurative thyroiditis
   - Chronic thyroiditis
4. **Iodide goiter**
   Long term administration of iodides ⟶↓↓ organification ⟶↑↑ TSH ⟶goiter
   E.g., Amiodarone (1/3 weight = iodine) ⟶ hypothyroidism& goiter
5. **Neoplastic**
   - Beign: Adenoma, teratoma
   - Malignant:
     - Follicular epithelium: Papillary, follicular& anaplastic
     - Parafollicular (C-cells): Medullary carcinoma
       - ☒ Sporadic
       - ☒ Familial (AD): Multiple endocrine neoplasia (MEN)
     - ❖ MEN type I: Parathyroid, Pancreas, Pituitary
     - ❖ MEN type IIA: Medulary carcinoma, Pheochromocytoma, Parathyroid
     - ❖ MEN type IIB: Medulary carcinoma, Pheochromocytoma, neuromas of mucous membranes (lips, tongue…)
6. **Developmental**
   - Thyroglossal cyst
   - Agenesis of one lobe (hyperplasia of the other)
7. **Congenital goiter** (may cause RD)
   - Defective hormone synthesis* (dyshormonogenesis)
   - Iodine deficiency*(maternal)& Iodine exposure*
   - Maternal medications (Amiodarone, methimazole, propylthiouracil)*
   - Thyroid hormone unresponsiveness*
   - Teratoma
   - Transient neonatal thyrotoxicosis (Congenital hypertyhroidism):
     - Type of the mother: Graves (active/ remission) or lymphocytic thyroiditis
     - Mechanism: Transplacental passage of TRSAb
     - C/P: Goiter, IUGR, irritability, exophthalmos, ↑↑ HR, HF, RD, hyperthermia
     - Treatment: IVF, propranolol, PTU ± Lugol's iodine ± digitalis
     - Prognosis: Transient. Most cases remit within 3-4 months

Solitary Thyroid Nodule

Etiology

1. **Simple nodular goiter** (with one palpable nodule)
2. **Lymphocytic thyroiditis** (with one prominent lymphoid follicle)
3. **Toxic nodule**
4. **Inflammatory nodule** (Abscess)
5. **Developmental**
   - Thyroglossal cyst
   - Agenesis of one lobe (hyperplasia of the other)
6. **Neoplastic**
   - Beign: Adenoma, teratoma
   - Malignant:
     - Follicular epithelium: Papillary, follicular& anaplastic
     - Parafollicular (C- cells): Medullary carcinoma

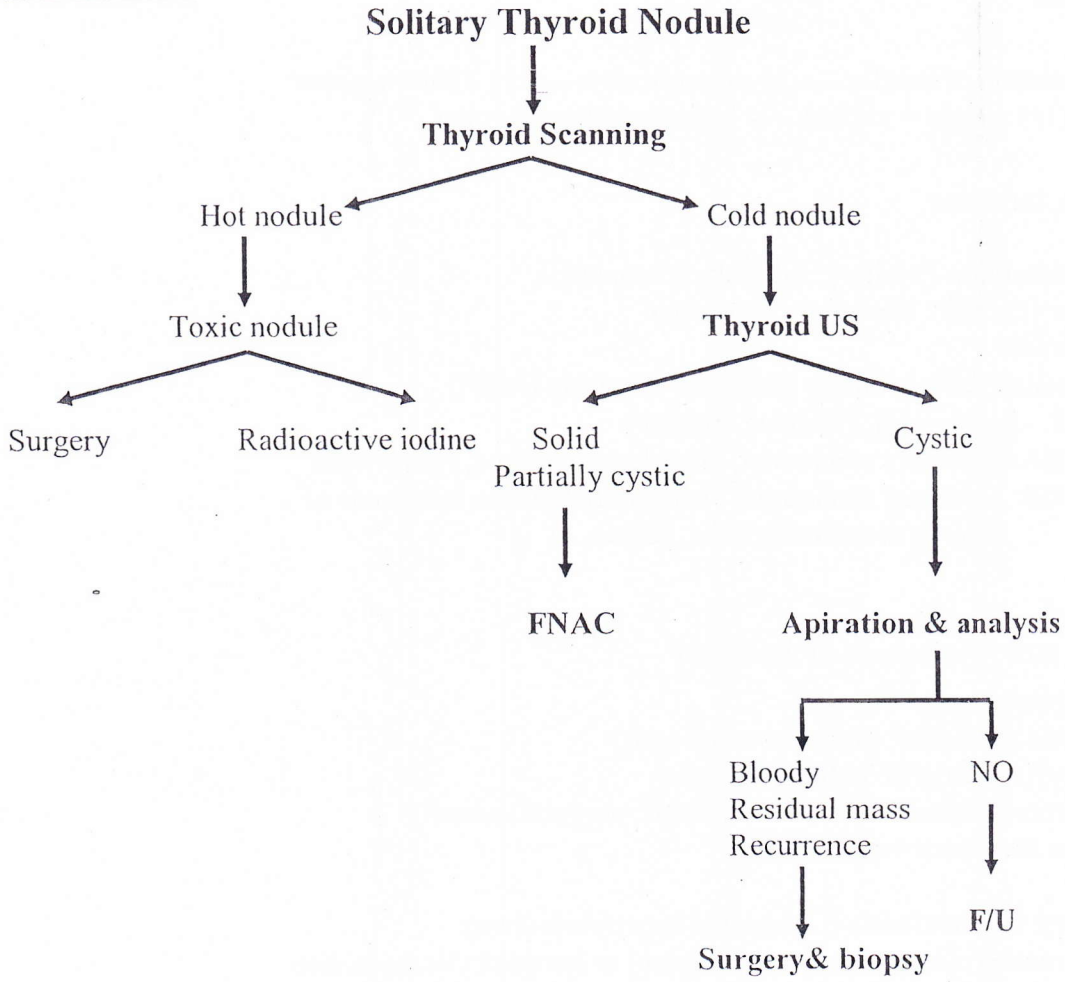
Diagnostic approach:

Clinical evaluation

- History
- Examination:

Most hot nodules are benign

Investigations



Glucose Homeostasis

Sources of blood glucose

1. Dietary carbohydrates (glucose, galactose, fructose)
2. Glycogenolysis (liver): Breakdown of glycogen into glucose or G-6-P
3. Gluconeogenesis: Synthesis of glucose from non-CHO sources (Lactate, pyruvate, proteins, glycerol, FA)

Removal of glucose from the blood

1. Tissue uptake: Glucose transporter (GLUT); may be insulin dependent (muscles & fat) or insulin independent (liver, β-cells, RBCs, brain)
2. Oxidation: mainly glycolysis followed by Krebs' cycle
3. Glycogenesis: Synthesis of glycogen from glucose
4. Lipogenesis: Synthesis of triacylglycerols (TAG) from CHO

} "Glucose Utilization"

Organs regulating blood glucose

1. GIT: prevents excessive hyperglycemia after a CHO meal
2. Liver: most important "glucostat"
3. Muscle & adipose tissue
4. Kidneys: prevent glucose loss "Renal threshold = 180 mg/dL"

Hormones regulating blood glucose

1. Insulin: The only hypoglycemic hormone (↑↑ uptake& utilization, ↓↓ production)
2. Adrenaline & glucagon
3. Glucocorticoids
4. GH
5. T_3& T_4

} Anti-insulin hormones

Overall regulation

1. CHO meal ⟶ ↑↑ blood glucose ⟶ ↑↑ insulin ⟶ ↑↑ uptake& utilization
2. Fasting ⟶ ↓↓ blood glucose ⟶ ↓↓ insulin &↑↑ anti-insulin ⟶ ↓↓ uptake& utilization and ↑↑ production (↑↑ glycogenolysis, ↑↑ gluconeogenesis)

Normal blood glucose

- Normally = 60-100 mg/dL (3.5-5.5 mmol/L). Serum is > whole blood readings, why?
- Fluorides are added to blood samples to # glycolysis which ↓↓ Blood glucose

Insulin

- It is a peptide hormone (51 aa), synthesized in the β-cells of the islets of Langerhans
- Proinsulin (= A chain + B chain + Connecting peptide "C-peptide") ⟶ Insulin
- The C peptide is secreted along with insulin (Index of the rate of insulin secretion)
- **Action:**
  - CHO⟶ ↑↑ Uptake & utilization, ↓↓ glycogenolysis, ↓↓ gluconeogenesis
  - Fats ⟶ ↑↑ Lipogenesis, ↓↓ lipolysis (breakdown of TAG into FA)
    ↓↓ ketogenesis (formation of ketone bodies)
    ↑↑ ketolysis (oxidation of ketone bodies into CO_2& H_2O)
  - Ptn ⟶ Anabolic
  - Potassium ⟶ Intracellular shift ⟶ ↓↓ K^+
- **Control of secretion:**
  - Stimulators: glucose, amino acids (e.g., arginine..), glucagons, ketone bodies, drugs (sulphonylurea)
  - Inhibitors: hypoglycemia, somatostatin, drugs (diazoxide)

Syndrome X (Metabolic syndrome) = Insulin resistance syndrome
Insulin resistance, Hyperinsulinemia, Obesity, Dyslipidemia & HTN

Diabetes Mellitus

Definition

It is a primary disturbance of CHO metabolism resulting from insulin deficiency, insulin resistance or both and characterized by hyperglycemia as a cardinal biochemical feature with secondary disturbance of fat & protein metabolism

Classification

A) **Type 1 DM:** (formerly called IDDM or juvenile diabetes)
Caused by insulin deficiency

B) **Type 2 DM:** (formerly called NIDDM or adult-onset diabetes)
Caused by insulin resistance with some degree of failure of insulin secretion

C) **Secondary diabetes:**
- Endocrinal: acromegaly, Cushing, hyperthyroidism, glucagonoma, somatostatinoma, pheochromocytoma
- Exocrine pancreas: Trauma, tumors, resection, hemochromatosis, Cystic fibrosis, pancreatitis, Pearson marrow pancreas syndrome
- Infections: CMV, congenital rubella, HUS
- Drugs: steroids, diazoxide, thiazides, β-adrenergic agonists, cyclosporine
- Genetic defects of β-cell function: MODY-1, MODY-2, MODY-3, MODY-4, 5, 6
- Genetic defects in insulin action: Type A insulin resistance, lipoatrophic DM
- Genetic syndromes:
  - Prader-Willi, Laurance-Moon-Beidel
  - Huntington chorea, myotonic dystrophy, Friedreich ataxia
  - Wolfram (DIDMOAD)
  - Down, Turner, Klinefelter

D) **Gestational diabetes:** Caused by
- Alimentary glucosuria
- Renal glucosuria
- Production of anti-insulin: estrogen, progesterone, cortisol, placental insulinase enzyme, human placental lactogen (hPL)

E) **Neonatal diabetes:**
- Transient : **a**-Without recurrence **b**-With recurrence 7-20 yrs later
  Onset: 1st week of life *Course:* spontaneous resolution within weeks/months
  Etiology: functional immaturity of β-cells
  C/P: SGA, hyperglycemia, glucosuria, dehydration, metabolic acidosis
  Rx: Intermediate-acting insulin 1-2 U/Kg/day bid
- Permanent: pancreatic agenesis

F) **Impaired glucose tolerance** (metabolic state intermediate between normal& DM)

Diagnostic criteria

Impaired glucose tolerance	Diabetes mellitus
Fasting plasma glucose = 110-125 mg/dL Or 2 hr plasma glucose (OGTT) < 200 mg/dL But ≥ 140 mg/dL	Fasting plasma glucose ≥ 126 mg/dL Or 2 hr plasma glucose (OGTT) ≥ 200 mg/dL Or Random plasma glucose ≥ 200 mg/dL + symptoms of DM (polyuria, polydipsia, loss of weight, glucosuria, ketonuria)

Type 1 Diabetes Mellitus

Definition

Diabetes mellitus caused by insulin deficiency due to destruction of pancreatic β-cells.

Etiology& Pathogenesis

Autoimmune response against β-cells in a **genetically predisposed** individual triggered by an **environmental** factor

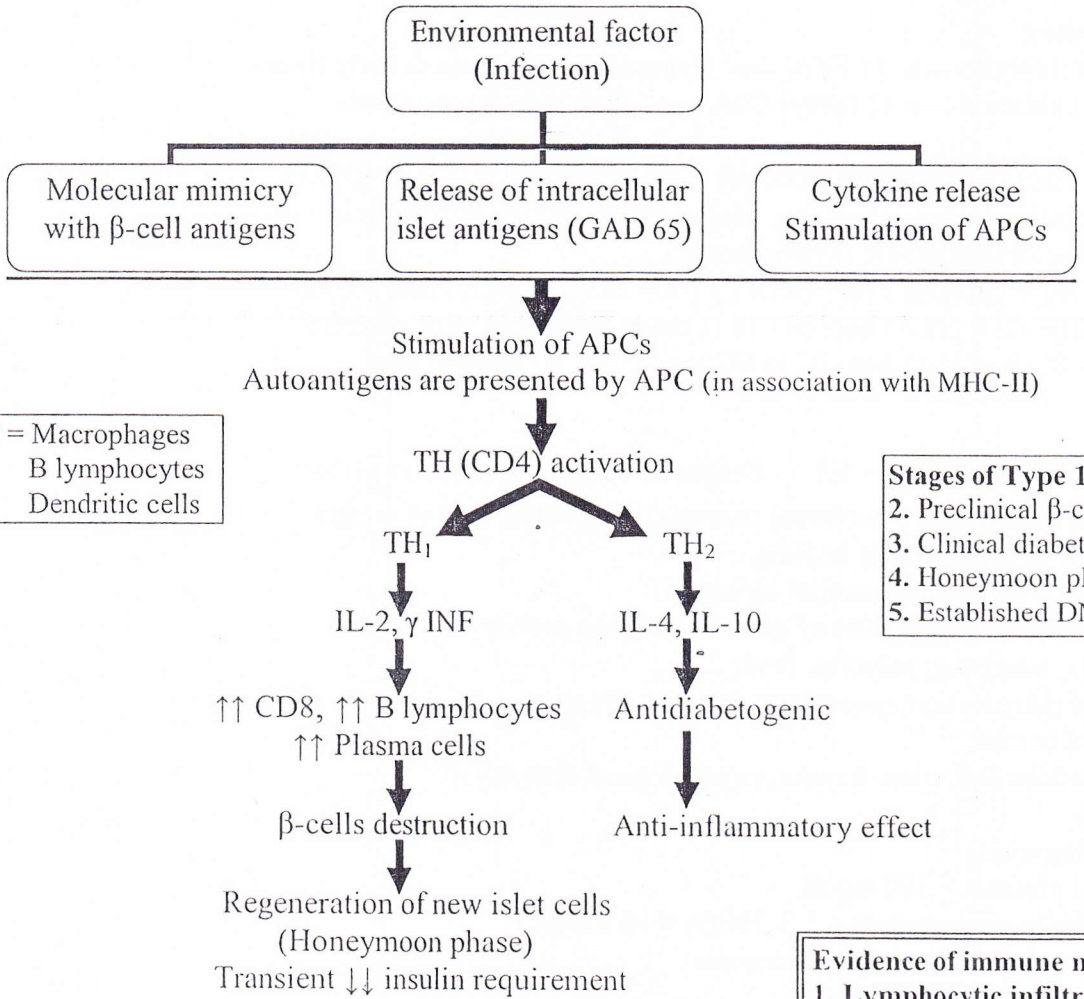
A) **Genetic predisposition:**

- HLA-DR3 or HLA-DR4 ⟶ ↑↑ Risk 2-3 folds
- Both HLA-DR3& HLA-DR4 ⟶ ↑↑ Risk 7-10 folds
- Absence of aspartate at position 57 of HLA-DQ β-chain ⟶ ↑↑ Risk 100 folds
- Presence of arginine at position 52 of HLA-DQ β-chain ⟶ ↑↑ Risk

B) **Environmental factors:**

- Viral infections: Coxsackie B3, B4, mumps, rubella, CMV
- Seasonal: autumn& winter (?? Due to ↑↑ risk of viral infections)
- Diet: cow's milk (molecular mimicry between bovine albumin & islet antigen 69)
- Chemicals: Rodenticides

C) **Autoimmune factors (=Pathogenesis of β-cell destruction):**



APC = Macrophages
B lymphocytes
Dendritic cells

Stages of Type 1 DM:
2. Preclinical β-cell destruction
3. Clinical diabetes
4. Honeymoon phase
5. Established DM

Pathology: Inflammatory cells infiltration

- 80-90% of β-cells are damaged at the onset
- Complete destruction follows within years

Evidence of immune nature:
1. **Lymphocytic infiltration** (CD4, CD8, B cells, Macrophage)
2. **Auto-Ab** (ICA, IAA, GADA)
3. **Associated disorders** (celiac, thyroid, pernicious anemia, Addison)

Prediction *(?? Done for high risk children)*

- HLA typing (DR3, DR4)
- Autoantibodies:
  - ☒ Islet cell antibody (ICA)
  - ☒ Insulin autoantibodies (IAA)
  - ☒ Glutamic acid decarboxylase (GAD65) antibodies (GADA)

Prevention

- Breastfeeding
- Vitamin D supplementation during infancy (?? Immunosuppressive effect)
- Immunosuppressives (Immunotherapy in *new-onset type 1 DM*):
  - ☒ Cyclosporin, azathioprine, prednisone, antithymocyte globulin (ATG)
  - ☒ Anti-CD3 monoclonal Ab (OKT3)

Pathophysiology

- **Hyperglycemia:** ↓↓ Insulin ⟶ ↓↓ Uptake& utilization & ↑↑ Production of glucose
- **Glucosuria:** when the renal threshold (180 mg/dL) is exceeded ⟶ osmotic diuresis ⟶ **polyuria& polydipsia**
- **Hunger & polyphagia:** ↓↓ Glucose uptake by the satiety center
- **Weakness:**
  - Inhibition of Krebs cycle (↓↓ ATP): due to ↓↓ oxaloacetate 2ry to ↓↓ glycolysis
  - Catabolic state
- **Delayed wound healing**
- ↓↓ Lipogenesis & ↑↑ lipolysis ⟶ ↑↑ FFA ⟶ **Hypertrigycerolemia & fatty liver**
- ↑↑ FFA ⟶ ↑↑ FA oxidation ⟶ ↑↑ acetyl-CoA ⟶ **Hypercholesterolemia**; ⟶ **Ketogenesis**
- **Acidosis:** due to ketosis (ketonemia& ketonuria) ⟶ Diabetic ketoacidosis **(DKA)**
- **Coma:** due to dehydration, hyperosmolality, acidosis& electrolyte disturbances
- **Hyperosmolality:** due dehydration& hyperglycemia
  Osmolality = 2 × Na + Glucose / 18 + BUN / 3 (*N = 285-295 mOsmol/Kg H_2O)*
  Effective osmolality = 2 × Na + Glucose / 18 (Urea is not an effective osmole)
- Hyperglycemia ⟶ Shift of H_2O from IC to EC space ⟶ **Hyponatremia**

Clinical picture

Age: usually 7-15 yrs **Sex:** ♀: ♂= 1:1 **Seasonal Variation:** more in winter

- Polyuria, polydipsia, nocturia, 2ry nocturnal enuresis, polyphagia, loss of weight
- Weakness, lethargy& delayed wound healing
- Pyogenic skin infection & vaginal monilial infection
- Diabetic ketoacidosis (DKA): (20-40% of diabetic children present with DKA)
  - Abdominal pain, vomiting, polyuria, fever
  - Clinical triad of dehydration, coma & acidotic breathing
  - Acetone odor of breath
  - Precipitating factors: infection, trauma, psychological disturbance
  - Mortality: 10%
  - **Laboratory diagnosis:**
    - ☒ Blood glucose > 300 mg/dL
    - ☒ Metabolic acidosis (pH < 7.3, HCO_3 < 16 mEq/L)
    - ☒ Ketonemia, Ketonuria & glucosuria
  - **DD:**

- Polyuria
- Nocturnal enuresis
- Acute abdomen (Medical & surgical causes)
- Dehydration
- RD
- Encephalopathy
- Stress hyperglycemia (No ketosis)
- Starvation ketosis (No hyperglycemia)

False results of HbA1c:
1. Blood loss
2. Abnormal β-chain (Thalassemia, Sickle)

Investigations

1. **Blood glucose:** (see diagnostic criteria)
2. **Glycosylated Hb (HbA1c):** It is formed by non-enzymatic linkage between glucose & β-chain of Hb. It gives an idea about the average blood glucose over the last 8-12 weeks (Long-term glycemic control)

Normal < 6 %, ***Good control*** = 6-8 %, ***Fair control*** = 8-10 %, ***Poor control*** ≥ 10 %

3. **Urine:** Glucosuria (DD: isolated renal glucosuria, Fanconi)
4. **OGTT:** Not routine
5. **Insulin level & C-peptide:** Marked ↓↓ (may be normal initially& in honeymoon phase)
6. **Autoantibodies, HLA**
7. **Screening of autoimmune diseases:** Thyroid, adrenal insufficiency, celiac
8. **Ophthalmologic examination:** (in children >10 yrs within 3-5 yrs of the onset)
   Fundus ⟶ Hemorrhage, exudates, vascular changes, vitreous Hge, retinal detachment
   Slit lamp ⟶ Cataract
9. **Microalbuminuria:** (Urinary albumin excretion rate (AER) = 30-300 mg/day)
10. **Quantitative sensory testing (QST) & nerve conduction velocity (NCV)**

Complications

A) Acute complications:

- DKA & Hyperglycemic hyperosmolar-nonketotic coma (HHNC)
- Hypoglycemia
- Hyperosmolality: Brain edema, myocardial depression, pulmonary edema, renal failure
- Brain edema: Iatrogenic during treatment of DKA or HHNC
- Arrhythmias: ↑↑ K, ↓↓ K, ↓↓ Ca

B) Long-term complications:

- Growth retardation (Mauriac syndrome: Short stature& hepatomegaly) "↓↓ Insulin"
- Syndrome of limited joint mobility: tight waxy skin & FTT
- Microvascular (prolonged DM >10 yrs)

☒ **Retinopathy**: Non-proliferative& proliferative diabetic retinopathy
Leading cause of blindness
Rx: Control of DM - Laser photocoagulation (Vitrectomy may be needed)

☒ **Nephropathy**:
Leading cause of ESRD
Microalbuminuria (early finding) followed by proteinuria, HTN & gradual ↓↓ KFT
Rx: Control of DM & HTN, Dietary protein restriction
Angiotensin-converting enzyme (ACE) inhibitors; e.g., Captopril

☒ **Neuropathy** (motor, sensory & autonomic)
Loss of HR variability (Early finding of autonomic neuropathy)
Rx: Control of DM – Aldose reductase inhibitors – Antioxidants – Carbamazepine

- Macrovascular
  - ☒ Coronary artery disease
  - ☒ Cerebrovacular disease
  - ☒ Peripheral vascular disease

Glucose ⟶ Sorbitol ⟶ Osmotic damage

C) Complications of insulin therapy:

- Lipodystrophy (atrophy & hypertrophy)
- Insulin allergy: local: erythema, pruritis
  Systemic: urticaria, angioedema
- Insulin resistance: Local tissue enzyme: **Rx**: addition of protease inhibitor to insulin
  Circulating Ab: **Rx**: ↑↑ insulin dose

Management of DKA

Effects of hyperosmolality:
1. Brain edema
2. Renal failure
3. Cellular disruption

Complications of Rx of DKA:
1. Hypoglycemia
2. Hypokalemia
3. Brain edema

With correction of blood glucose
→ ↓↓ Osmotic diuresis
→ Rapid rehydration

Rapid ↓↓ of effective osmolality
→ ↑↑ Risk of brain edema

Aim of treatment

- Expansion of intravascular volume
- Correction of electrolyte& acid base status
- Initiation of insulin therapy

Clinical assessment

- Conscious level & neurological signs
- Vital signs
- Hydration status (shock, degree of dehydration)
- Acidotic breathing (Rapid & deep)
- Urine output (bag not catheter)
- Infection, vomiting& hematemesis

Prepare 2 IV lines& Order lab for

- Evidence Blood glucose
- Electrolytes (Na,K,Cl,Ca,Mg,P)
- Osmolality
- Serum β (OH) butyrate
- Corrected Na = Na +1.6× (BG-100) /100
- Blood gases
- BUN& creatinine
- Effective osmolality = 2Na + Glucose/18
- Urine for ketones
- Sepsis screen for infection

Fluid& electrolyte therapy

A) Shock therapy:
If the patient is shocked → Anti shock 10-20 ml/Kg (NS or Ringer L) over 30 min

B) Deficit requirement: (according to the degree of dehydration)

	< 30 Kg (< 8 yrs)	> 30 Kg (> 8 yrs)
Mild dehydration	50 ml / Kg	30 ml / Kg
Moderate dehydration	100 ml / Kg	60 ml / Kg
Severe dehydration	150 ml / Kg	90 ml / Kg

C) Maintenance requirement: (1500 ml / m^2 / day)

D) Total working fluids (Shock + Deficit + Maintenance): given over 36 hrs
- 1/2 → over 12 hours (Shock therapy is subtracted from the 1st half)
- 1/2 → over the next 24 hours
- Maximum amount should not exceed 4 L/m^2/ day
- Type of fluid:
  Blood glucose > 300 → NS
  Blood glucose 250-300 → G 5 %: NS 1:1 (If acidosis is corrected)
  → G10 %: NS 1:1 (If acidosis is not corrected)
- Correction of hyperglycemia occurs well before acidosis. Therefore, insulin is still needed to control FA release& acidosis. So, glucose must be added to allow further continuous insulin infusion
- Duration of fluid therapy: Continued till
  a. Correction of dehydration & acidosis
  b. Tolerance of oral intake (sips of H_2O then soft diet)
- In severe hyperosmolality (>340), the total fluid is given over 48 hrs
- In severe hyperosmolality & high corrected Na, half NS is used after 1st 2 hrs

E) Potassium

Potassium is added if initial serum k is < 6 mEq/L & the patient voids urine

It is better to give K partly as phosphate (↑↑ 2,3 DPG, KCl ↑↑ acidosis)

Serum K (mEq/L)	pH > 7.1	pH < 7.1
5 - < 6	10 mEq/L	15 mEq/L
4 - 5	20 mEq/L	25 mEq/L
3 - 4	30 mEq/L	35 mEq/L
< 3	40 mEq/L	45 mEq/L

F) Bicarbonate therapy *(rarely needed)*

a. pH < 7 ⟶ 40 mEq / m^2

b. pH < 6.9 ⟶ 80 mEq / m^2

HCO_3 Therapy ↑↑ Risk of brain edema

G) Phosphate

If serum phosphate < 0.5 mmol/L, add 30 mmol / L $NaPO_4$ over 8 hrs

H) Magnesium

If serum magnesium < 0.5 mmol/L, add 30 mmol / L $MgSO_4$ over 8 hrs

Insulin therapy

- **Prepare** insulin infusion: 50 U regular insulin + 500 ml NS (1 ml = 0.1U) or (50 + 50)
- **Flush** the plastic tube with 50 ml
- **Use** infusion pump
- **Rate:** 0.1 U / Kg / hr (1 ml / kg / hr) **without a bolus**. When blood glucose decrease to < 300 mg% half the dose
- **Satisfactory** ↓↓ in blood glucose: 10% of the initial BG to maximum of 100 mg/dL/hr
- If bl. glucose ↓↓ more rapidly ⟶ half the rate of insulin infusion
- If bl. glucose does not ↓↓ over 2 hrs ⟶ double the rate of insulin infusion
- In case of ***hypernatremia*** (corrected Na >145 mEq/L) prepare insulin as 1:1
  250 U regular insulin + 250 ml 1/2 NS (1 ml = 1U)
- **Duration** of insulin therapy: Continued till
  a. Correction of dehydration& acidosis (pH >7.2 HCO3 >10 mEq/L)
  b. Tolerance of oral intake (No vomiting)
- **Then shift to SC regular insulin** (started 1/2 hr before D/C of IV insulin)
- **Lifelong SC insulin** should be 0.5-1 U/Kg/day, divided as:
  - 40% Intermediate insulin (1/2 before breakfast, 1/2 before dinner)
  - 60% Regular insulin (1/3 before each meal)

Monitoring

- **Clinical status**
- **Signs of brain edema:** Give mannitol…
- **Blood glucose** hourly, then every 2 hours (when SC insulin is started)
- **Blood gases & electrolytes** every 2 hrs (in the 1st 8 hrs), then every 4 hrs
- **Na trend**
  a. Positive Na trend: Corrected Na ↑↑ by 1.6 mEq/L for every 100 mg% ↓↓ glucose
  b. Negative Na trend: Corrected Na does not↑↑ or even ↓↓ with ↓↓ glucose
  This indicates accumulation of free water with ↑↑ risk of brain edema
  Management: Slow the rate of IVF (given over 48 hrs)

Long-Term Management

A) Insulin therapy

a. Dose: average 0.5-1 U/Kg/day according to pubertal status
Children in the honeymoon phase require **only** 60-70% of the full replacement dose

b. Types of insulin: (Recombinant DNA)

	Example	Onset	Peak	Duration
Short acting	Regular insulin ***(Actrapid 40, 100)***	1/2-1 hr	1-2 hr	6-8 hr
	Lispro& Aspart ***(Novorapid)***	Much rapid with short *tail effect*		
Intermediate acting	Isophane insulin (NPH) ***(Insulatard 40, 100)***	1-2 hr	10 hr	24 hr
Long acting	Ultralent ***(Insuman)***	7 hr	16 hr	36 hr
	Glargine insulin ***(Lantus)***	Flat 24-hr profile *(once daily)*		

c. Regimen: (Three-injection regimen is commonly used)
- 40 % Intermediate insulin (1/2 before breakfast, 1/2 before dinner)
- 60 % Regular insulin (1/3 before each meal)

Ideal regimen = **Basal-bolus regimen** "Glargine + Lispro / Aspart"
(More physiologic with better glycemic control & ↓↓ risk of hypoglycemia)

d. Technique:
- Insulin syringes with fine needles calibrated in units
- SC injection with 90° angle to the skin
- Change the site regularly to prevent local complications (lipodystrophy)
- Short acting insulin should be drawn first
- Proper storage of vials (Refrigerator)

e. Monitoring of blood glucose:
- Self-monitoring of blood glucose (SMBG): At least 3-4 times/ day using blood glucose strips (Visual or glucometer)
- Continuous glucose monitoring systems (CGMS): using SC sensor
- Glycosylated hemoglobin (HbA1c)

f. Adjustment of dosage:
- Adjustment of dosage is based on blood glucose readings (SMBG)
- Target glucose level = 100-140 mg%
- Any change should be in the range of 10-15% "Extra-dose"
- With infections: ↑↑ the dose of insulin to avoid DKA
- With exercise: ↓↓ the dose of insulin to avoid hypoglycemia

g. Other methods:
- Insulin pump: (Continuous SC insulin infusion)
  - Programmed "basal-bolus"
  - More physiologic with more flexibility in timing of meals& snacks
  - Single needle injection every 3 days
  - Disadvantages: improper dosage
- Inhaled insulin (still under trial ?? pulmonary fibrosis)
- Oral insulin (still under trial)
- Pancreas& islet transplantation
- Regeneration of islets

B) **Dietary management** (Essential component of management)

- Number of meals: 3 main meals (breakfast, lunch & dinner) and 2 snacks
- Special pamphlets are available
- CHO counting is widely used in many centers (Each point = 15 g = 0.5-1 U)
- There are few dietary restrictions (even sweets & simple sugars are not totally forbidden)
- Non-nutritive sweeteners: Saccharine (? Cancer UB), Aspartame [Avoid Sorbitol, why?]

<table>
<tr><th></th><th colspan="2">Requirements& Comments</th></tr>
<tr><td>Calories</td><td colspan="2">75-100 Cal/Kg/day
CHO =55%, Fat =30%, Protein =15%</td></tr>
<tr><td>CHO</td><td colspan="2">Complex CHO are preferred (starch products)
High fiber content (grain)
Avoid simple sugars, sweets& carbonated beverages</td></tr>
<tr><td rowspan="2">Fats</td><td>Encourage</td><td>Avoid (restrict)</td></tr>
<tr><td>Fats of plant origin
Margarine
Vegetable oil
Fish& chickens</td><td>Fats of animal origin
Butter
Animal oil
Fatty meats</td></tr>
<tr><td>Proteins</td><td colspan="2">High protein intake may contribute to diabetic nephropathy
Lower end of normal range is preferred 15%</td></tr>
</table>

C) **Exercise**

- Regular exercise ↑↑ insulin receptors. Vigorous exercises may precipitate DKA
- No form of exercise is contraindicated.
- Risk of hypoglycemia is ↓↓ by ↓↓ insulin dose&↑↑ food intake prior to exercise

D) **Basic education& emotional support**

Hypoglycemic Reactions

Etiology

1. ↑↑ Insulin dose
2. ↑↑ Exercises (specially sustained exercises e.g., running)
3. ↓↓ Calories
4. Honeymoon phase (Transient ↓↓ insulin requirement)

Clinical picture

A) ↑↑ **Catecholamines:** Tachycardia, palpitation, pallor, sweating, tremors
B) **Cerebral glucopenia:** Headache, hunger, drowsiness, confusion, coma, convulsions

Treatment *(Urgent)*

1. CHO drinks
2. IV fluids
3. Glucagon
4. Search for a cause (adjust insulin dose)

Brittle Diabetes

Definition

Unexplained wide fluctuations in B.G. in spite of high dose insulin, often with recurrent DKA

Etiology

Psychological or psychiatric problems (eating disorders, dysfunctional family dynamics)

Treatment (Supportive)

Somogyi Phenomenon
Dawn Phenomenon

Definition
Early morning hyperglycemia

Classification

	Dawn Phenomenon	Somogyi Phenomenon (rare)
Manifestation	**Early morning hyperglycemia** (before breakfast)	
	Without preceding hypoglycemia	With preceding late night or early morning hypoglycemia
Pathogenesis	Overnight production of GH ↓↓ insulin level	Hypoglycemia → ↑↑ anti-insulin → hyperglycemia
Diagnosis	Continuous glucose monitoring systems (CGMS)	

Nonketotic Hyperosmolar Coma

Definition & Clinical picture

It is as syndrome characterized by:
1. Severe hyperglycemia > 600-800 mg %
2. Hyperosmolarity > 350 mOsmol/Kg H_2O
3. Severe dehydration (Osmotic diuresis)
4. Lactic acidosis
5. No or mild ketosis (residual insulin is *sufficient* to # Ketogenesis)
6. Neurological manifestations: disturbed conscious level, motor deficits (hemiplegia...), why?

Dehydration
–
Acidosis
Hyperosmolarity

Etiology (Not **peculiar** to DM)

A) Disease states:
1. DM
2. Head trauma
3. Severe infection & dehydration

B) Iatrogenic:
1. Drugs: Catecholamines, diazoxide, steroids
2. Suprasellar surgery
3. TPN

Treatment

A) Fluid& electrolyte therapy

Total working fluids (Shock + Deficit + Maintenance): given over 36 hrs
- 1/2 → over 12 hours (Shock therapy is subtracted from the 1st half)
- 1/2 → over the next 24 hours
- Type of fluid:
  - Blood glucose > 300 → NS (or 1/2 NS)
  - Blood glucose 250-300 → G 10 %: 1/2 NS 1:1

Rapid correction of dehydration

Slow correction of osmolarity

B) Insulin therapy
- **Prepare** insulin infusion: 50 U regular insulin + 500 ml NS (1 ml = 0.1U)
- **Flush** the plastic tube with 50 ml
- **Use** infusion pump
- **Rate:** 0.05 U/Kg/hr (0.5 ml/kg/hr) without a bolus. Start with the 2nd hour of IV fluid

C) Monitoring *(as in DKA)*

Type 2 Diabetes Mellitus

Definition

Diabetes mellitus caused by insulin **resistance** with progressive defect in insulin **secretion**

Etiology & Pathogenesis

	Type 1 DM	Type 2 DM
Formerly called	IDDM or juvenile	NIDDM or adult-onset DM
Incidence	2 : 1000	Increasing (parallel to obesity epidemic) 30% of new DM cases
Age	7-15 yrs (any age)	Older age (rapidly ↑↑ in children)
Sex	Equal	♀ > ♂
Body weight	Usually thin	Usually obese
Onset	Rapid	Insidious
Cause	Insulin deficiency	Insulin resistance (some degree of failure of insulin secretion)
Pathology	Pancreatic β-cells damage	Various degrees of β-cells impairment
Pathogenesis	Autoimmune destruction of β-cells	No evidence of immune disturbance
Insulin level	↓↓ or absent endogenous insulin	Relative hyperinsulinemia (but *lower* than control subjects)
Genetic component		Stronger, polygenic (aggravated by environmental factors)
Concordance	30-50% in identical twins	Almost 100% in identical twins
Susceptibility	HLA linked (DR3, DR4…)	Not HLA linked
Auto-Ab	ICA, IAA, GADA	May be +ve
Associated diseases	Thyroiditis, Celiac, Addison	Obesity, dyslipidemia, HTN (Metabolic $)
DKA	30% at presentation	Infrequent (stress, infection)
Need to insulin	Necessary (to prevent DKA)	Occasional
Acanthosis nigricans	Absent	Present in the majority

Prevention

1. Change dietary habits& ↑↑ physical activity
2. Screening of high-risk children (Obese with +ve family history of DM)

Metabolic $
= Insulin resistance $
Insulin resistance
Hyperinsulinemia
Obesity
Dyslipidemia
HTN

Treatment

1. Nutritional education
2. Weight reduction
3. Metformin (↓↓ Hepatic glucose production). CI in renal & liver impairment (*Cidophage*)

Impaired Glucose Tolerance

Definition

It is metabolic state intermediate between normal glucose homeostasis& DM. It is not a disease but risk factor

Diagnosis Oral Glucose Tolerance Test (OGTT). See the table

Indications of OGTT:
1. Glucosuria
2. Hyperglycemia (sress, steroid)
3. At-risk (obese& +ve family)

Treatment

Weight reduction
Diagnosis & Rx of other risk factors

Parathyroid Glands

Calcium Homeostasis

Sources

Milk, cheese, yogurt

Corrected Ca = actual Ca + 0.8 (4 - albumin)

Blood Calcium

A) **Non-diffusible (45%):** Bound to albumin& globulin. It is physiologically inactive

B) **Diffusible:**

a. **Non-ionized (5%):** Forming complexes with citrate, bicarbonate, PO_4…

b. **Ionized (50%):** It is the physiologically active form

Hypoalbuminemia (e.g., Nephrotic $) ⟶ ↓↓ Total Ca with normal ionized Ca (No tetany)
Hyperphosphatemia (↑↑ PO_4) (e.g., Renal failure) ⟶ ↓↓ Ionized Ca (tetany)
The product of Ca x P = constant [Solubility product]

Hormonal Control of Ca & Phosphate metabolism

↓↓ **Mg** ⟶ ↓↓PTH release + ↑↑PTH resistance

A) **Parathyroid hormone (PTH):** "↑↑ Serum Ca level"

1. Intestine: ↑↑ Ca absorption indirectly through ↑↑ vitamin D
2. Kidney: ↑↑ Ca reabsorption, ↑↑ PO_4 excretion & ↑↑ 1α hydroxylase enzyme (↑↑ Vit. D)
3. Bones: ↑↑ Ca mobilization from bones (↑↑ Osteoclast number & activity)

B) **Vitamin D:** "↑↑ Serum Ca level"

1. Intestine: ↑↑ Ca absorption, ↑↑ PO_4 absorption
2. Kidney: ↑↑ Ca reabsorption, ↑↑ PO_4 reabsorption
3. Bones: Normal mineralization of bones. Excess vit. D ⟶ ↑↑ Ca mobilization from bones

C) **Calcitonin:** "Little effect on serum Ca level"

1. Produced by the parafollicular cells of the thyroid gland
2. ↓↓ Ca mobilization from bones (↓↓ Osteoclast number & activity)
3. Important for fetal skeletal growth

D) **Thyroid hormones& GH:** "↑↑ serum Ca level"

E) **Glucocorticoids:** "↓↓ Serum Ca level"

Anti-vit. D effect (↓↓ Ca intestinal absorption) ⟶ Osteoporosis

Normal blood Calcium

Total Ca = 9-11 mg/dL = 2.25-2.75 mmol/L = 4.5-5.5 mEq/L
Ionized Ca = 4.5-5.5 mg/dL = 1.1-1.3 mmol/L = 2.25-2.75 mEq/L

Hypocalcemia

Causes of vitamin D deficiency:
1. ↓↓ Intake, ↓↓ Sun exposure
2. ↓↓ Absorption (Steatorrhea, anticonvulsant therapy)
3. ↓↓ Activation (Liver, renal)
4. Vit.Ddependent rickets (type I, II)

Etiology

1. **Hypoparathyroidism**
2. **Pseudohypoparathyroidism**
3. **Vitamin D deficiency:** (See rickets)
4. **Hypomagnesemia:** Malabsorption (generalized& isolated)
   ↑↑Renal loss (HereditaryAD,drugs; aminoglycosides,amphotericin B)
5. **Hyperphosphatemia:** CRF, tumor, phosphate therapy
   a. ↑↑ Intake: Cow's milk, laxatives
   b. ↓↓ Excretion: Renal failure
   c. Trancellular shift: Tumor lysis $, rhabdomyolysis, acute hemolytic crisis
6. **Drugs:** Bisphosphonates, calcitonin…
7. **Others:** Acute pancreatitis, massive blood transfusion, citrated blood

Hypoparathyroidism

Definition

Deficient production of PTH or its action

Etiology

1. Transient hypofunction:

- **a.** Early neonatal hypocalcemia: 12-72 hrs [Common in Preterm, IDM, Asphyxia]
- **b.** Late neonatal hypocalcemia: D3- D7 [Functional immaturity of the parathyroid glands]
- **c.** Transient idiopathic hypocalcemia: 1-8 weeks [Functional immaturity …]

2. Maternal hyperparathyroidism (Mechanism: as in hypoglycemia of IDM)

Maternal hypercalcemia → Fetal hypercalcemia → Fetal ↓↓ PTH → Neonatal hypocalcemia

3. Aplasia of the parathyroid glands

- **a.** DiGeorge syndrome: Defect in development of 3rd & 4th pharyngeal pouches
  Aplasia of thymus & parathyroid glands [Hypocalcemia & immunodeficiency]
  Genetics: Microdeletion (22q) Diagnosis: FISH
  C/P: Neonatal hypocalcemia, T cell deficiency (Viral, candida, chronic diarrhea, FTT)
  Facies: Fish mouth, Flat face, short Filtrum & hypertelorism
  Cardiac: Conotruncal anomalies (Interrupted aortic arch, truncus arteriousus)
- **b.** Other syndromes with 22q deletion: Velocardiofacial $, Conotruncal-face $,
  CATCH 22 $ [Cardiac, Abnormal facies, Thymic hypoplasia, Cleft palate, Hypocalcemia]

4. XLR Hypoparathyroidism

5. AR Hypoparathyroidism

6. AD Hypoparathyroidism: Activation mutation of Ca sensing receptors

7. HDR syndrome: Hypoparathyroidism, Deafness & Renal anomalies

8. Immune

- **a.** Isolated
- **b.** Type I autoimmune polyendocrinopathy "HAM" (Hypoparathyroidism, Addison, mucocutaneous candidasis)

9. Mitochondrial diseases

Kearns-Sayer syndrome (KSS)

10. Iatrogenic

Surgical removal during thyroidectomy

11. Idiopathic Hypoparathyroidism

End-organ Resistance

12. Pseudohypoparathyroidism = Albright hereditary Osteodystrophy (End organ R.)

- **a.** Type IA: Defect in the PTH receptor
  Tetany + Skeletal + Mental retardation + BG calcification + Infertility (# TSH & GTH)
- **b.** Type IB: Defect in the adenyl-cyclase system
- **c.** Type II: Defect in the cell response to cAMP

Diagnosis of PHP:

↓↓ Ca, ↑↑ PO_4, ↑↑ Alkaline phosphatase, ↑↑ PTH

Response to exogenous PTH:

Exogenous PTH → ↑↑ Ca, ↓↓ PO_4, ↑↑ cAMP (True hypo-)
Exogenous PTH → No ↑↑ cAMP (Type I)
Exogenous PTH → ↑↑ cAMP (Type II)

Skeletal manifestations of PHP:

1. Short stature
2. Stocky build (Obesity)
3. Short fingers (Brachydactyly) specially 3rd & 4th
4. Index is longer than middle finger
5. Exostosis & bowing

Pseudopseudohypoparathyroidism = C/P of PHP + Normal Ca & PO_4

Clinical picture

(A) Tetany

a. Latent tetany: diagnosed by provocative tests

- ☒ *Chvostek's sign:* Tapping of the Facial nerve ⟶ Contraction of the facial muscles
- ☒ *Trousseau's sign:* Compression of the upper arm ⟶ Carpal spasm
- ☒ *Erb's sign:* Electrical stimulation with low Galvanic current ⟶ Muscle contraction
- ☒ *Peroneal sign:* Tapping of the peroneal nerve near the fibula ⟶ Pedal spasm

b. Manifest tetany

- ☒ Irritability & parasthesia
- ☒ Twitches & convulsions (Carpo-pedal spasm)
- ☒ Laryngismus stridulus
- ☒ Risus sardonicus & trismus (Spasm of the facial muscles)

(B) Ectodermal changes:

a. Skin: Dry & rough
b. Nail: Brittle with horizontal white lines
c. Teeth: Hypoplastic
d. Lens: Cataract

(C) Picture of the cause: Addison, mucocutaneous candidasis…

Investigations

☒ **Laboratory:**

1. ↓↓ Ca (N = 9-11 mg/dL)
2. ↑↑ PO_4 (N = 3.5-6.5 mg/dL)
3. ↓↓ or normal alkaline phosphatase (N = 130-420 U/L)
4. ↓↓ PTH
5. Exogenous PTH ⟶ ↑↑ Ca, ↓↓ PO_4, ↑↑ cAMP (blood & urine)

☒ **Imaging:**

- X-ray: ↓↓ Bone density
- ECG: Long QT interval
- EEG: Slow activity
- CT brain: Basal ganglia calcification

Treatment

Monitoring of HR is essential
Stop if bradycardia occurs

↓↓ Mg should be considered in any case of tetany not responding to IV Ca

(A) Emergency treatment of convulsions

a. IV Calcium gluconate 10%: (1 cc/Kg) slowly
b. IV Magnesium sulphate 10%: (1 cc/Kg)
c. Oral calcitriol (1,25 dihydroxycholecalciferol)
Initial dose: 0.25 µg/day
Maintenance: 0.01-0.1 µg/Kg/day (max: 2 µg/day)

(B) Maintenance:

a. Oral Calcium gluconate (Hi-Cal syrup)
b. Dietary phosphate restriction: Milk, cheese, yogurt
c. Oral calcitriol (1,25 Dihydroxycholecalciferol): 0.01-0.1 µg/Kg/day (Max = 2 µg/day)
d. 1α hydroxycholecalciferol: 0.05-0.1 µg/Kg/day

Hypercalcemia

Etiology

1. **PTH excess**
   a. Primary hyperparathyroidism
   b. Tertiary hyperparathyroidism
   c. Ectopic PTH production "malignancy"
   d. Maternal Hypoparathyroidism

2ry hyperparathyroidism = Normal or ↓↓ Ca

2. **Vitamin D excess**
   a. Iatrogenic
   b. Sarcoidosis, TB, subcutaneous fat necrosis (inflammatory disorder of adipose tissue)
3. **Excess Ca intake:** Milk-alkali syndrome
4. **Endocrinal causes**: Thyrotoxicosis, Addison's disease
5. **Malignancy:** PTH-related peptide (PTHrP) secreting tumors (Paramalignant syndrome)
6. **Drugs**: Thiazides
7. **Others**:
   a. **Prolonged immobilization**
   b. **Idiopathic hypercalcemia of infancy**
   c. **Williams syndrome**
      Genetics: Microdeletion (7q)
      Diagnosis: FISH
      C/P: Neonatal hypercalcemia, elfin facies (small mandible, upturned nose), mental retardation, supravalvular aortic stenosis & social personality
   d. **Familial hypocalciuric hypercalcemia:** (AD with 100% penetrance)
      Inactivation mutation of Ca sensing receptors in the kidney & parathyroid gland
      ↑↑ Ca + normal or mildly ↑↑ PTH + ↓↓ urinary Ca/Creatinine ratio
      C/P: usually asymptomatic discovered accidentally on routine investigations
   e. **Hypophosphatasia**
   f. **Metaphyseal chondrodysplasia:** activation mutation of PTH receptors

Hyperparathyroidism

Definition

Increased level of PTH

Etiology

(A) Primary Hyperparathyroidism "↑↑ PTH, ↑↑ Ca"

1. Adenoma
2. MEN type I: Parathyroid (adenoma / hyperplasia), Pancreas, Pituitary
3. MEN type IIA: Medulary carcinoma, Pheochromocytoma, Parathyroid
4. Neonatal Hyperparathyroidism
5. Transient Neonatal Hyperparathyroidism (2ry to Maternal hypoparathyroidism)
   Maternal hypocalcemia ⟶ Fetal hypocalcemia ⟶ Fetal ↑↑ PTH ⟶
   Transient neonatal hyperparathyroidism
6. Familial hypocalciuric hypercalcemia

(B) Secondary Hyperparathyroidism: (compensatory 2ry to *hypocalcemia*) "↑↑PTH, ↓↓ Ca"

1. CRF
2. Vitamin D deficiency

(C) Tertiary Hyperparathyroidism "↑↑ PTH, ↑↑ Ca"

It is autonomous parathyroid hyperplasia in longstanding 2ry hyperparathyroidism

(D) Pseudohypoparathyroidism (PHP) "↑↑ PTH, ↓↓ Ca"

Clinical picture *(of hypercalcemia)*

a. **Bones:** Weakness, bony pains, pathological fractures
b. **Stones:** Renal stones, renal colics, hematuria, **polyuria**, polydipsia, renal failure
c. **Abdominal groans:** Acute pancreatitis, anorexia, nausea, vomiting, constipation
d. **Psychic moans:** Depression & psychosis,
e. **Fatigue overtone:** Weakness
f. **Parathyroid crisis** (Ca > 15 mg%): Oliguria, renal failure, coma, convulsions

Investigations

☒ **Laboratory:**

1. ↑↑ Ca (N= 9-11 mg/dL)
2. ↓↓ PO_4 (N= 3.5-6.5 mg/dL)
3. ↑↑ or normal alkaline phosphatase (N= 130-420 U/L)
4. ↑↑ PTH *(done simultaneously with Ca)*

PTH is decreased in all cases of hypercalcemia except in:
- Hyperparathyroidism
- Familial hypocalciuric hypercalcemia

☒ **Imaging:**

- X-ray: Subperiosteal bone erosion of phalanges, bone cysts (osteitis fibrosa cystica)
- ECG: short QT interval
- Abdominal US: Renal stones & nephrocalcinosis
- Neck US, CT, subtraction scintigraphy: for localization of parathyroid adenoma

Treatment

1. Surgical exploration + intraoperative selective venous sampling:
   a. Adenoma: Removal
   b. Hyperplasia: Total parathyroidectomy
2. Postoperative observation for the development of Hypoparathyroidism
3. Treatment of acute hypercalcemia:
   a. Hydration (IV fluids)
   b. IV bisphosphonate (↓↓ Osteoclasts)
   c. Steroids (prednisone): effective in hypercalcemia of sarcoidosis, vit. D intoxication, malignancy & SC fat necrosis [**not** in hyperparathyroidism]

Comprehension Questions

[31.1] A 3650-g term infant has ambiguous genitalia, including an enlarged clitoris/microphallus and one palpable testis in the labioscrotal folds. Sonogram reveals a uterus and ovaries. Which of the following is the most likely explanation for the child's ambiguous genitalia?

A. Aromatase deficiency
B. Congenital adrenal hyperplasia
C. Female pseudohermaphroditism
D. Male pseudohermaphroditism
E. True hermaphroditism

[31.2] A mother brings in her 1-week-old son who has vomited four times over the last 24 hours. He has no fever or diarrhea. The infant is breast-feeding poorly and is "floppy" per mom. He has had only one wet diaper in the last 12 hours. Physical examination reveals a lethargic infant who has lost 250g since birth, with pulse of 110 bpm, dry oral mucosa, and no skin turgor. Which of the following tests would be reasonable to consider after stabilization and electrolyte measurement?

A. Serum cortisol level
B. Urine cortisol level
C. Serum 21-hydroxylase level
D. Serum 17α -hydroxyprogesterone level
E. Serum testosterone level

[31.3] A mother brings in her 15-year-old daughter because she has never started her periods. She otherwise is healthy and takes no medications. Her past medical history is unremarkable except for inguinal hernia repair as an infant. Family history is unremarkable. She is at the 75th percentile for height and weight, has Tanner stage IV breast development, and no pubic or axillary hair development. Her anogenital examination reveals a short, pocketlike vaginal opening. Which of the following is the most likely explanation for her amenorrhea?

A. Adrenal tumor
B. Congenital adrenal hyperplasia
C. Pituitary tumor
D. Testicular feminization
E. Turner syndrome

Management of DKA

Aim of treatment:

- Expantuion of intravascular volume
- Correction of electrolytes & acid base status
- Intiation of insulin therapy

Clinical assessment

- Conscious level &neurological signs.
- Vital signs
- Hydration status(shock – degree of dehydration).
- Acidotic breathing (rapid and deep)
- Urine output (urine bag not catheter)
- Infection, vomiting &hematemesis.

Prepare 2 IV lines & order lab for

Blood glucose Blood gases
Electrolytes (Na, K, Cl, Ca, Mg & P).BUN &creatinine.
Osmolarity& effective Osmolarity
Corrected Na = measured Na + (2 x BG- 100)/100.
Urine for ketones.
Serum β OH butyrate & lactate.Sepsis screen for infection.

Fluid& electrolyte therapy

A-Shock therapy: If shocked ➔antishock **10** ml /kg (NS / Ringer L)

B-Deficit requirement;

	□*8 yrs*	□*8yrs*
Mild dehydration	**50** ml/kg	**30** ml/kg
moderatedehydration	**80** ml/kg	**50** ml/kg
Severe dehydration	**100** ml/kg	**80** ml/kg

C-Maintenance requirement;

0-2yrs.	**80 ml/k/d**
2-6yrs.	**70 ml/k/d**
6-10yrs.	**60ml/k/d**
10-14 yrs.	**50ml/k/d**
>14 yrs.	**35 ml/k/d**

D-The total working fluids (*shock + deficit + maintenance*): given over **48 hrs**.

× Shock therapy should be subtracted from the total.

- **Types of fluids given:**
  - If blood glucose >***300***→ NS
  - Blood glucose ***250-300***;

→ 0.9NS: G**5%** 1:1 (acidosis is **corrected**)

→ 0.9NS: G**10%** 1:1 (acidosis is **not corrected**)

➢ *Correction of hyperglycemia occurs well before acidosis. Therefore, insulin is still needed to control FA release & acidosis. So, glucose must be added to allow further continuous insulin infusion.*

- **Duration of fluid therapy:** continued till
  a) Correction of dehydration & acidosis.
  b) Tolerance of oralintake (sips of water then soft diet).

In severe hyperosmolality (>340), the total fluid is given over 72 hrs.
In severe hyperosmolality &high corrected Na, half NS is used after 1ST6 hrs.

E) Potassium:

K is added if initial serum k<**5**mEq/L& the patient voids urine as follows:

Serum K (mEq/L)	**pH>7.1**	**pH< 7.1**
5- <6	10 mEq/L	15 mEq/L
4-5	20 mEq/L	25 mEq/L
3-4	30 mEq/L	35 mEq/L
<3	40 mEq/L	45 mEq/L

F) Bicarbonate therapy*(rarely needed):*

- If PH < 7give➲**40**mEq/m^2
- If PH < **6.9** give➲**80**mEq/m^2

Insulin therapy

- **Prepare** insulin infusion:**50**U regular insulin +**500** ml NS (1ml= 0.1 U) or (50 + 50)
- **Use** infusion pump.
- **Rate:0.1 U/Kg/hr**(1ml/kg/hr) ***without a bolus***. When blood glucose decrease to **<300** mg % → half the dose.
- **Satisfactory**↓in bl. glucose: 10% of the initial BG to a maximum of 100mg/dl/hr.
- If blood glucose drops more rapidly → half the rate of insulin infusion.

- If blood glucose does not drop over 2 hrs→double the rate of insulin infusion.
- In cases of ***hypernatremia*** (corrected Na >**155**mEq/L), prepare insulin as 1:1
  250U regular insulin+250ml 1/2 NS (1ml = 1U).
- **Duration** of Insulin therapy : continued till
  a. correction of dehydration &acidosis(pH >7.3& HCO3 >15 mEq/L)
  b. Tolerance of oral intake (no vomiting)
- **Then shift to SC regular insulin**(started ½ hour before D/C of IV insulin).
- **Lifelong SC insulin** should be**0.5- 1U/kg/day**, divided as:
  ➔40% intermediate insulin (½ before breakfast & ½ before dinner).
  ➔ 60% regular insulin($^1/_3$ before each meal).

MONITORING

- ❑ Clinical status.
- ❑ Signs of brain edema: give mannitol.....
- ❑ Blood glucose: every hour, then every 2 hours when SC insulin is started.
- ❑ Blood gases & Electrolytes: every 2 hours(in the first 8 hrs), then every 4 hrs
- ❑ Na trend: the change in Na with the change of blood glucose.
  a) *Positive Na trend*: corrected Na ↑ by 2mEq/L for every 100mg%↓glucose.
  b) *Negative Na trend:*corrected Na does not ↑ or even↓ with ↓ of glucose
  This indicates accumulation of *free water* with ↑ risk of brain edema
  Management; slowthe rate of IVF (over **72**hrs).

Endocrinology

1. A child aged 10 days has ambiguous genitalia. Which of the following is correct:

   a. Buccal smear shows chromatin negative
   b. Raised urinary 17-ketosteroids
   c. Genotype 45 XO would reliably explain the anomaly
   d. Klinefelter's syndrome is the most likely diagnosis
   e. Sex of rearing is strongly determined by the chromosomal sex

2. Which of the following doses of prednisolone is equivalent in its glucocorticoid potency to 20mg of hydrocortisone:

   1. 2 mg
   2. 5 mg
   3. 10 mg
   4. 15 mg
   5. 20 mg

Dexamethasone is roughly 30 times more potent than hydrocortisone

3. A 15 year old girl is referred by her GP with agitation and weight gain. She has no past medical history of note. Her mother was treated for an 'overactive thyroid' and now she takes thyroxine tablets. Examination reveals no specific abnormalities with a BP of 112/70 mmHg. Investigations reveal the following results:

   TSH 3.2 mU/L (0. 35 - 5.0)
   Total T4 250 nmol/L (55 - 144)
   Free T4 12.9 pmol/L (9 - 24)
   Total T3 3.2 nmol/L (0. 9 - 2.8)
   Free T3 3.8 pmol/l (3.0-5.8)
   What is the most likely explanation for her condition:

   1. Bulimia Nervosa
   2. Dysthyroglobulinaemia
   3. Factitious Thyrotoxicosis
   4. Graves' Disease
   5. Pregnancy

4. The thyroid hormone receptor is:
   1. A gated ion channel
   2. A cell surface receptor
   3. A cytoplasmic protein
   4. A G-protein coupled receptor
   5. A nuclear receptor

5. A 16 yr old ♀ patient is referred with1ry amenorrhoea. Investigations reveal a 46XY karyotype. What is the most likely diagnosis:

1. Turner's syndrome
2. Maternal androgen administration during pregnancy
3. Noonan syndrome
4. Testicular feminisation syndrome
5. 5-α-reductase deficiency

6. 7 yr old ♂ who was operated upon for a craniopharyngioma, which of the following disorders can be expected over the next few years:

1. Diabetes mellitus
2. Hyponatraemia
3. Poor growth
4. Precocious puberty
5. Spastic diplegia

7. Which one of the following findings would not be expected in an 18 month old infant with poorly controlled hypothyroidism:

1. High plasma TSH concentration
2. Delayed bone age
3. Umbilical hernia
4. Diarrhea
5. Delayed development milestones

8. A 16 year old ♀ presents with hypertension and increasing weight. Which of the following features would be most suggestive of Cushing's syndrome rather than exogenous obesity:

1. Abdominal striae
2. Acanthosis Nigricans
3. Buffalo Hump (interscapular fat pad)
4. Moon face
5. Proximal myopathy

9. Which ONE of the following is true concerning ADH:

1. Its excess may cause hyponatremia
2. Ethanol potentiates it's release
3. It is a steroid hormone
4. It acts on the proximal convoluted tubules
5. It is synthesized in the posterior pituitary